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GIANT FOLLICULAR LYMPHADENOPATHY WITH OR WITHOUT SPLENOMEGALY

ITS TRANSFORMATION INTO POLYMORPHOUS CELL SARCOMA OF THE LYMPH FOLLICLES AND ITS ASSOCIATION WITH HODGKIN'S DISEASE, LYMPHATIC LEUKEMIA AND AN APPARENTLY UNIQUE DISEASE OF THE LYMPH NODES AND SPLEEN — A DISEASE ENTITY BELIEVED HERETOFORE UNDESCRIBED

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There is a comparatively newly recognized form of disease involving the lymph nodes and spleen that has been designated generalized giant lymph follicle hyperplasia of lymph nodes and spleen,[1] generalized follicular lymphadenopathy with splenomegaly, and so on.[2] In this paper the title of the disease has been modified for reasons which will appear obvious as the text develops. Except for certain important histologic modifications, giant follicular lymphadenopathy is, I believe, an expression of the same variety of hyperplasia of the lymph follicles in the superficial and other nodes as that which occurs in localized or regional lymphadenopathies associated with long-continued drainage of irritants. Clinically, the condition bears a noteworthy resemblance to Hodgkin's disease, lymphosarcoma and lymphatic leukemia. Histologically, it is different from all of them in that the enlarged nodes show replacement of their normal architecture by dimensional and numerical hyperplasia of the follicles, sometimes with similar alterations in the follicles of the spleen (fig. 1). The cases are separable into two groups: first, those in which the hyperplastic follicles in the nodes and spleen maintain their structural identity for months or years, or the nodes may undergo reduction in size or disappear temporarily for no apparent reason, or they may show histologic signs of healing irrespective of

From the Department of Pathology, Bellevue Hospital.

1. Brill, N. E.; Baehr, G., and Rosenthal, N.: J. A. M. A. **84**:668, 1925.
2. Symmers, D.: Arch. Path. **3**:816, 1927.

treatment, or they may rupture spontaneously and heal; second, those cases in which the condition alters its course, as is shown in this paper, I believe, for the first time. In the latter group (*a*) the lesion may undergo direct transformation into a polymorphous cell sarcoma, or (*b*) it may become associated with the histologic changes of Hodgkin's disease, or (*c*), with the changes of lymphatic leukemia, or (*d*) with those of an apparently unique disease characterized, among other things, by late necrotic lesions in the follicles of lymph nodes and the spleen. In still other instances the combination of giant follicular lymphadenopathy, polymorphous cell sarcoma and Hodgkin's disease may be observed in the same lymph node.

Up to the present moment a sufficient number of cases has been collected to demonstrate that giant follicular lymphadenopathy, although not well known, is not rare and that it is of clinical importance, largely for the reasons that it is easily recognized histologically and is usually rapidly submissive to mild roentgen therapy, to which it may remain amenable over an expanse of time such as to indicate prolongation of life. Its associated lesions in the form of polymorphous cell follicular sarcoma, Hodgkin's disease and lymphatic leukemia are more antagonistic to roentgen therapy. Indeed, in giant follicular lymphadenopathy the quick response of the lymph nodes to mild roentgen therapy is so impressive that if, at a later date, recurrence is noted and readjustment of the enlarged nodes is delayed or incomplete or both, and larger doses are required, one would seem to be justified in suspecting that the condition is undergoing some form of mutation.

In assembling these cases for publication, a great deal of detail has been omitted. Only those facts are included which seem to me to have a possible bearing on a disease entity whose ramifications probably reach far beyond the limits of this venture in descriptive pathology.

In order to avoid repetition of histologic description, cells which are derived from the germinal centers of the lymph follicles are divided into two main forms and are referred to (*a*) as large hypochromatic embryonal cells, or shadow forms, and (*b*) as hyperchromatic embryonal cells of the large lymphocytic type (fig. 4). Forms transitional between the two are discernible. Either of the two main varieties may be encountered in practically pure form, both in the hyperplastic follicles and in the polymorphous cell sarcoma derived from them, but often admixtures occur in which one or the other form predominates.

(*a*) The nuclei of the hypochromatic embryonal follicular cells are so poor in chromatin as to resemble shadows. They are relatively very large and are rounded or oval. The nucleus occupies almost all of the cell body and is sometimes indented or boat shaped, especially in the transitional forms. Often the cell body is not visible. At other times.

the nucleus lies in a pinkish-staining syncytial bed. The nucleus possesses a delicate but distinct membrane, a scanty, gossamer-like, irregularly broken chromatic network and often a nucleolus or nucleolus-like body.

(*b*) The hyperchromatic embryonal follicular cells of the large lymphocytic type are larger than the large lymphocytes, are usually ovoid and have a relatively richly chromatic, often indented, sometimes irregularly stippled nucleus, with or without a minute quantity of light pinkish-staining cytoplasm.

(*c*) Special stains reveal no reticulum cells although reticulum fibers may be present in greater or less numbers.

I. GIANT FOLLICULAR LYMPHADENOPATHY WITH OR WITHOUT SPLENOMEGALY

PREVIOUSLY RECORDED CASES

Possibly the first case of this description to be recorded was that of Becker.[3] He did not recognize its import but included it as an interesting case in a report of several others of the same general nature.

The case was that of a woman aged 33 whose illness commenced with swelling of the lymph nodes of the neck, followed in the course of the next three years by enlargement of all the superficial lymph nodes, some of which reached the size of a walnut. The spleen was massively enlarged. A solitary lymph node removed three years after the onset was found to present the histologic signs of "simple hyperplasia." No mention is made of the presence of hyperplastic lymph follicles. The red blood cell count was 4,500,000; the hemoglobin content, 70 per cent. The white blood cell count was 9,400, with polymorphonuclear neutrophils 44 per cent, lymphocytes 51 per cent, eosinophils 3 per cent, mononuclear and transitional cells 0.8 per cent and mast cells 0.3 per cent.

Becker was inclined to classify the condition under the heading of pseudoleukemia, which at that time, 1901, in Germany and elsewhere was commonly used to include almost any form of otherwise unexplainable enlargement of the lymph nodes and spleen.

Brill, Baehr and Rosenthal[1] described 2 cases almost identical with that recorded by Becker.

The first case was that of a woman aged 28 who presented generalized enlargement of the superficial lymph nodes, the nodes varying in size from that of a pea to that of a walnut; the nodes were movable and free from tenderness. Roentgen examination showed moderate enlargement of the peribronchial nodes, particularly on the left side. The spleen was huge, reaching from the level of the eighth rib on the left side to the anterior-superior iliac spine and to the right for a distance of 5 cm. beyond the midline; it was smooth and not tender. Microscopic examination by Mandlebaum of lymph nodes excised from the neck and axilla "failed to show any evidence of Hodgkin's disease, lymphosarcoma

3. Becker, E.: Deutsche med. Wchnschr. **27**:726, 1901.

or tuberculosis." The changes were confined to excessive enlargement of the lymph follicles. Under roentgen therapy the splenic and lymph node enlargements disappeared.

The second case was that of a woman aged 32 who complained of gradual enlargement of the abdomen of two months' duration. Both spleen and liver were greatly enlarged, the spleen extending from the eighth intercostal space above the brim of the pelvis below and to within 2 cm. of the midline. The cervical, axillary, epitrochlear and inguinal nodes were moderately enlarged. Because of weakness, progressive anemia and evidences of blood destruction, splenectomy was performed. Microscopic examination of the spleen and of an enlarged lymph node removed from the abdomen showed enormous hyperplasia of the lymph follicles in both. Three months after splenectomy the lymphadenopathy disappeared, and the blood picture returned to normal. Later, the nodes in both axillae became enlarged but under roentgen therapy the enlargement disappeared.

The paper by Brill, Baehr and Rosenthal was the first, as far as I know, to call attention to the occurrence of a condition of disease without specific changes in the blood characterized by generalized lymphadenopathy due to numerical and dimensional hyperplasia of the lymph follicles and to emphasize its clinical importance and its amenability to roentgen therapy.

In 1927 I published a report of 3 cases of an apparently identical character.[2]

The first was that of a man aged 32 who in 1921 presented moderate generalized superficial lymphadenopathy with splenomegaly. Biopsy of the enlarged inguinal nodes revealed no noteworthy changes other than excessive hyperplasia of the lymph follicles. Nine years later the patient died of Hodgkin's disease. Further details are presented later in this paper.

My second case was that of a girl aged 7 who was admitted to Bellevue Hospital because of swollen lymph nodes which had been present in various parts of the body for a period of two and one-half years. At the time of admission, the suboccipital, cervical, axillary, inguinal and femoral nodes were enlarged. The nodes varied in size from 1 to 3 cm. and were firm and discrete. The spleen was palpable two thirds of the distance from the xiphoid to the umbilicus; it was firm and smooth and not tender. Shortly after admission, enlarged lymph nodes were removed from the inguinal and cervical regions and on microscopic examination I found no alterations in them other than marked numerical and dimensional hyperplasia of the lymph follicles.

A third case was that of a Spaniard aged 33, a laborer, who was admitted to the service of Dr. C. J. MacGuire, at St. Vincent's Hospital, complaining of "stomach trouble" and mild jaundice, both of about six months' duration. Physical examination revealed moderate jaundice, together with numbers of enlarged lymph nodes in both axillae, more evident on the right side, and palpable lymph nodes in both inguinal regions. The nodes were discrete, freely movable and painless; they measured approximately from 1 to 1.5 cm. in diameter. The spleen was felt 6 cm. below the costal margin on the left side, and the liver was palpable at the level of the umbilicus. Dr. MacGuire thought it advisable to undertake an abdominal exploration. He found an immense growth of lymph nodes in the retroperitoneal region. The lymph nodes were closely packed and varied in size from 1 to 6 cm. Numerous enlarged lymph nodes were observed in the

vicinity of the common bile duct; compression by these nodes was thought to have caused the jaundice by obstruction of the biliary drainage system.

An enlarged lymph node removed from the abdomen measured 5 by 3 by 1 cm. and presented on section a smooth, coarsely granular, or finely nodular, cream-colored substance. Histologic examination revealed extraordinary hyperplasia of the lymph follicles, both numerical and dimensional, and moderate streaklike interfollicular fibrosis.

Neither of the latter 2 patients was subjected to roentgen therapy. Both disappeared from observation and could not be traced.

Terplan,[4] in 1929, contributed a case under the heading "A Peculiar Granuloma-like Systemic Disease."

A white woman 61 years of age died about nine months after the onset of an illness characterized by emaciation, dyspnea followed by orthopnea, edema of the lower extremities and of the region of the sacrum, generalized enlargement of the superficial lymph nodes and massive enlargement of the spleen. At necropsy the cervical nodes were found to be individually about "the size of a bean," as were most of the axillary and superclavicular nodes, although in occasional instances they reached the proportions of a "small prune." The superficial and deep inguinal nodes were from "bean to hazelnut size," occasionally "the size of a prune." The retroperitoneal nodes were enlarged, some of them forming clusters the "thickness of one's finger"; others were discrete and ranged in size from that "of a cherry to that of a hazelnut." The spleen measured 20 by 13 by 8 cm. and showed innumerable grayish follicles.

Histologic examination revealed numerous greatly enlarged, pale staining lymph follicles in all of the nodes, superficial and deep, in the interstitial tissues of the liver and in the bone marrow and spleen. Most of the follicles were isolated, others were confluent, and still others formed curious arrangements—clover leaf, dumbbell or kidney shaped.

NEW CASES

CASE 1.—A man aged 40 was admitted to Bellevue Hospital Oct. 16, 1933, to the service of Dr. Charles Nammack and of Drs. Ira Kaplan and Sidney Rubenfeld. He complained of a sensation of burning in the feet of seventeen weeks' duration. This was so severe that he had to sleep with his feet beneath a tent arranged at the foot of the bed.

The spleen was enlarged to a point 15 cm. below the left costal margin. It was firm but not tender. The submandibular, epitrochlear, inguinal and axillary nodes on both sides were enlarged to the extent of from 1 to 2 cm. and were discrete, firm and without sign of tenderness. The liver was palpable 1 finger-breadth below the right costal margin. Numerous blood counts showed nothing worthy of note except leukopenia, with white cell counts varying from 5,650 to 1,900, and on occasions eosinophilia, with counts of from 4 to 12 per cent.

Histologic examination of a group of excised lymph nodes showed widespread numerical and dimensional hyperplasia of the follicles with circumferential condensation of small lymphocytes and interfollicular fibrosis (fig. 1). The follicles were composed largely of hyperchromatic embryonal cells of the large lymphocytic type.

4. Terplan, K.: Verhandl. d. deutsch. path. Gesellsch. **24**:65, 1929.

Roentgen therapy was commenced, and the patient was given 800 roentgens to the anterior and posterior splenic areas every other day for a total of eight exposures. He was examined every three months during the following three years and was free from any sign of lymph node or splenic enlargement until May 1937, when it was found that the spleen was barely palpable. He complained of a feeling of slight fatigue but was otherwise well and continued to work at his trade as a tile layer. He is still well after a period of four years and six months.

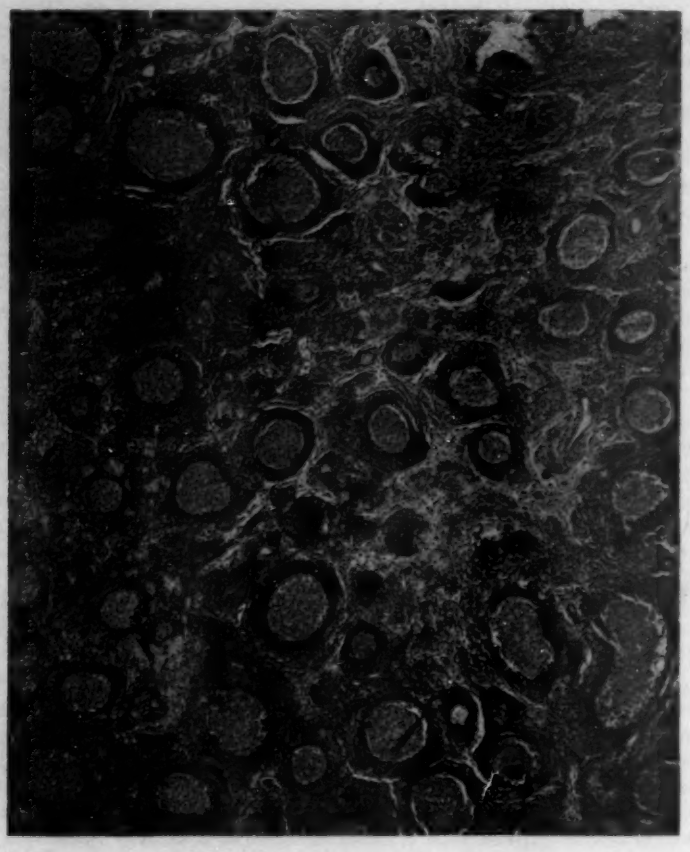

Fig. 1 (part I, case 1).—Very low power photomicrograph, showing numerical and dimensional hyperplasia of the lymph follicles in giant follicular lymphadenopathy, with an extensive degree of interfollicular fibrosis.

Case 2.—A woman aged 19, a dietitian, had from early childhood suffered from episodes of sore throat and tender protruding lymph nodes in the neck near the angle of the jaw. At 4 years of age her tonsils and adenoids were removed because they almost met in the middle line and breathing was difficult. Intermittent attacks of sore throat accompanied by enlargement of lymph nodes in the neck continued until the patient was 16 years of age. At that age she

left the damp climate in which she lived and went to college in a high, dry altitude. Her throat troubles ceased. In 1927 the patient stated that she had had in the right groin a solitary enlarged lymph node that was about the size of an egg, firm and tender. She remained at rest in bed three weeks, and the swollen node disappeared and never returned. In March 1936 she observed three nodes in the right axilla. These nodes were tender, and each was about 2 cm. in diameter and from time to time became larger. One of them eventually ruptured, discharged thin cream-colored puslike material for a period of about three weeks and healed. She suffered similar experiences on two subsequent occasions about a month apart. She stated that otherwise she felt perfectly well and was able to attend to her duties without inconvenience or discomfort.

Examination early in September 1936 revealed a moundlike mass of lymph nodes that obliterated the supraclavicular fossa on the right side. The nodes approximated twenty-five or thirty in number, were discrete and measured from 1 to 3 cm. in diameter. A smaller mass was present in the left supraclavicular fossa, the individual nodes measuring about 2 cm. in diameter and approximating ten or twelve in number. They were discrete and not tender. On either side of the neck beneath the middle of the jaw was a solitary lymph node, which measured about 1 cm. in diameter and was rounded, movable and not tender. The axillary lymph nodes on both sides were enlarged to the number of five or six and were not tender. Each node measured about 2 cm. in diameter. The spleen and liver were not palpable.

A group of five enlarged lymph nodes was removed from the left axilla in September 1936. The nodes varied in diameter from 1 to 4 cm. and were separated by filmy investments of connective tissue. The cut surface was smooth, homogeneous, glistening and faintly brownish.

On microscopic examination the lymph nodes showed almost complete replacement by massive lymph follicles, some of them so large as to fill the entire low power field of the microscope. In places the follicles were closely packed; in other places they were separated by collections of small lymphocytes. Most of the follicles were rounded or oval; others, elongated or boat shaped. The germinal centers stained lightly and were composed almost exclusively of hyperchromatic embryonal cells of the large lymphocytic type with a slight admixture of large hypochromatic cells.

The blood counts were normal.

Under roentgen therapy, consisting of 100 roentgens every week for a period of five weeks, the enlargement of the lymph nodes disappeared. At the present moment (August 1938) the patient is apparently perfectly well except for a small solitary node in the neck, about 1 cm. in diameter, and is pursuing her work as a dietitian.

Case 3.—The patient was a married woman aged 28, referred by Dr. F. E. Coster, Hamilton, Ontario, Canada, and Dr. William J. Deadman, director of laboratories, Hamilton General Hospital.

The patient complained that during the past four years she had been annoyed by lymph node enlargements in both sides of the neck and in the axillae, groins and femoral regions. The nodes gradually increased in size until the summer of 1936, when sudden increase in those of the neck caused her to consult Dr. Coster. The spleen was not palpably enlarged. The patient stated that otherwise she felt perfectly well.

The blood picture was normal.

A solitary lymph node removed for biopsy showed replacement by enormous numbers of lymph follicles, each surrounded by a zone of small lymphocytes. Some of them were so massive as to overflow the low power field of the micro-

scope. Many of them assumed abnormal forms—top shaped, hook shaped, boat shaped and the like. For the greater part they were closely set, and the intervening cells were small lymphocytes. The germinal centers were made up almost completely of hyperchromatic embryonal cells of the large lymphocytic type.

Roentgen treatment of high voltage was given as follows: Jan. 18, 1937, 300 roentgens to the neck and to the axillae; January 21, 300 roentgens to the abdomen, groin and mediastinum; February 22, 300 roentgens to the right side of the neck and 300 to each axilla. Under this therapy the nodes were greatly reduced but the enlargement had not disappeared March 17.

Case 4.—A man was referred from St. John's Hospital, Brooklyn, through Dr. T. J. Curphey, and from Bellevue Hospital, service of Dr. Guilford Dudley. This patient was observed from July 16, 1935 to April 1937. In December 1934 he noticed in both axillae about a dozen enlarged lymph nodes, which he described as being individually about the size of a peanut. Two months later he noticed three or four enlarged nodes in the right groin, each the size of a bean, and in the left groin a solitary node about the size of a small marble. On both sides of the neck were three or four enlarged nodes, each of them about the size of a small prune, enlarged preauricular nodes, each the size of a large marble, and one submental node, the size of a split pea. The supraclavicular nodes on both sides were enlarged to the number of about fifteen, each the size of a small marble. In April 1935 he was treated by a series of roentgen ray exposures, following which there was disappearance of the enlargement of almost all of the nodes, which marked diminution in the size of the others.

Clinically, in July 1935, the abdomen was protuberant, and a fluid wave was felt. The spleen was palpable 3 fingerbreadths below the left costal margin in the nipple line. The liver was below the costal margin on the right side. There was pitting edema of the lower extremities. Two days after admission, thoracentesis released 400 cc. of cloudy yellow fluid. During the next six weeks, five thoracenteses were done with withdrawal of 1,700, 1,500, 2,000, 2,500 and 2,000 cc. of fluid, respectively.

Reexamination Dec. 28, 1936, showed a solitary node lying in the midline of the neck behind the symphysis of the lower jaw, measuring 3 cm. in length and 1 cm. in breadth. There were similarly enlarged solitary nodes in the axillae and groins, measuring approximately 2 cm. in diameter.

Microscopic examination of a lymph node removed in December 1934 showed excessive hyperplasia of the lymph follicles. Some of them were demarcated by a rim of small lymphocytes; others were practically bereft of lymphocytic zones. Some of them were closely set; others were separated by collections of small lymphocytes. Many of them were enormous, others were considerably above the average size, while a few were of limited dimensions. They varied in shape, some being rounded, others irregularly rounded, some oval, others elongated or kidney shaped. In many instances they were fused to form huge masses filling the low power field of the microscope. The germinal centers were made up largely of loosely packed large hypochromatic embryonal cells together with an admixture of hyperchromatic embryonal cells of the large lymphocytic type. An occasional eosinophil was seen among the small lymphocytes in the interfollicular spaces.

The solitary lymph node remaining in the right side of the neck in April 1937 was removed, and microscopic examination revealed giant follicular lymphadenopathy with almost precisely the same histologic changes as those encountered in the node removed in December 1934.

Roentgen therapy was instituted in the usual small doses, but because of apparent resistance of the nodes larger amounts were given. In the course of about three weeks the enlargement disappeared practically completely, except that one node in the right side of the neck remained moderately enlarged. This was removed, and the microscopic appearances were as described in a foregoing paragraph.

The patient was admitted to Bellevue Hospital April 23, 1937, complaining of a severe nonproductive cough, hoarseness and weakness. At this time it was noted that the fingers were clubbed. The blood count was normal.

At the present moment (Aug. 1, 1937) the patient is free from detectable enlargements of the lymph nodes, and the spleen is not palpable.

CASE 5.—A man aged 34, a metal worker, married, a patient of Dr. Walter Schmidt, of Cliffside, N. J., was referred by Dr. F. J. Fadden Jr., pathologist to the Englewood Hospital, Englewood, N. J. This patient first became aware of enlargement of the lymph nodes in the preauricular regions in the spring of 1936. Otherwise he was apparently in perfect health. The nodes were present to the number of four or five on each side and were rounded or elongated, firm, freely movable and from 1 to 2.5 cm. in diameter. A chain of similarly enlarged nodes, about eight in number, extended from the mastoid to the clavicle on both sides of the neck. Some of them, six or eight, were from 4 to 5 cm. in diameter. Enlarged nodes were present in both axillae, numbering from eight to ten and measuring from 2 to 5 cm. In the groins and along the upper mesial sides of both thighs were a few nodes, each enlarged to the extent of 2 cm. The spleen was not palpable.

The blood count was normal.

An enlarged lymph node was removed from the neck Feb. 5, 1937. Microscopic examination showed massive hyperplasia of the lymph follicles, most of which were round or oval and circumscribed by small lymphocytes. The germinal areas were composed practically exclusively of hyperchromatic embryonal cells of the large lymphocytic type.

Roentgen therapy was given over the period between Feb. 20 and March 27, 1937, with treatments spaced at intervals of one week. Four doses of 375 roentgens each were given over the neck and axilla on each side. Enlargement of the nodes disappeared. At the present time (Nov. 28, 1937) the patient's condition remains unchanged.

CASE 6.—A white man aged 41, a painter, admitted to the Second Surgical Division of Bellevue Hospital Oct. 16, 1936, was referred by Dr. Guilford Dudley, director. He complained of diarrhea of two weeks' duration, abdominal cramps and frequent nocturia, weakness, and vomiting on three occasions. He stated that he had lost 9 pounds (4 Kg.) in weight in the past two weeks.

Physical examination gave essentially negative results except that the lymph nodes in the axillae and in the inguinal regions were palpable. The blood showed: red cells, 4,070,000; hemoglobin content, 90 per cent; white cells, 9,150, polymorphonuclears, 41 per cent. A complete differential count was not made. The roentgenologist's report follows: "There is an irregularly ragged defect in the middle third of the transverse colon, measuring 5 cm., indicating an organic infiltration, probably malignant."

The patient was operated on by Dr. Dudley, November 17, who failed to find abnormal changes in the intestine or elsewhere apart from enlarged lymph nodes around the cecum and in the mesentery of the small intestine and transverse mesocolon. The nodes were described by Dr. Dudley as present "literally by

hundreds." Each was enlarged to about "the size of a pea" and shelled out readily. The liver and spleen were apparently normal. Three nodes were removed for microscopic examination.

The patient was readmitted March 19, 1937, and discharged April 27. He complained of an epigastric hernia. At operation for correction of the hernia numerous enlarged lymph nodes were found in the transverse mesocolon and in the mesentery. Many enlarged nodes were felt in both axillae. Nodes were removed from the transverse mesocolon, the mesentery and the right axilla for microscopic examination. The nodes removed from the transverse mesocolon measured 3 by 2 by 1 cm.; those from the right axilla measured, respectively, 0.1 by 1 by 0.5 cm. and 6 by 5 by 3 mm., and those from the mesentery measured, respectively, 1 cm. and 8 mm. in diameter.

Microscopic examination of the nodes removed from the abdomen and both axillae showed essentially the same change, namely, extensive numerical and dimensional hyperplasia of the lymph follicles, almost every one of the latter being sharply delimited by a wall of small lymphocytes, while the germinal areas were composed of large hypochromatic, or shadow cells, and hyperchromatic cells of the large lymphocytic type together with transitional forms.

The patient was admitted to Bellevue Hospital for the third time May 5, because of bloody stools and intractable diarrhea. Examination of the stools revealed Endamoeba histolytica. The patient was treated with emetine hydrochloride and left the hospital July 20, free from all signs of dysentery.

Comment.—It is possible that the widespread intra-abdominal lymphadenopathy was secondary to the amebic dysentery, although the presence of myriads of hyperplastic nodes in the abdomen and of enlarged peripheral nodes in association with that disease is contrary to necropsy experience in 16 cases at Bellevue Hospital. In 3 of the 16 cases the abdominal lymph nodes were enlarged to a moderate extent because of hyperemia and edema. If in the case just recorded the association of amebic dysentery was a coincidence, it remains that the distribution of the enlarged nodes and the hyperplastic follicular alterations in them are in keeping with the changes in giant follicular lymphadenopathy of unknown origin. If amebic dysentery stood in causative relationship to giant follicular lymphadenopathy of the abdominal, axillary and inguinal nodes, the association lends support to the view that the changes in giant follicular lymphadenopathy are of "toxic" or "inflammatory" origin. It is unfortunate, of course, that there was no tissue available for examination from any of the abdominal or peripheral nodes in this patient following the cessation of dysentery.

In this case, the great preponderance of lymph node enlargements was in the abdomen, and in this manner the case combines with the third case published in a previous paper and synopsized in this paper to emphasize the fact that the origin of giant follicular lymphadenopathy is not necessarily confined to the superficial nodes.

CASE 7.—A woman aged 33, married, a seamstress, was admitted to the Physicians' Hospital, Queens, N. Y., July 25, 1936, and died at Queens General Hospital April 3, 1937. She had been referred by Drs. Alfred Angrist and Julius Blankfein, of Flushing, N. Y. At 15 years of age this patient suffered from influenzal pneumonia which incapacitated her for a period of two or three months. During early life she complained often of sore throat, and tonsillectomy was performed when she was 20. In 1928 she contracted a cold which was followed by frontal sinusitis. At that time she felt two symmetrically located "lumps,"

each about the size of an olive, in the back of her neck, on each side of the midline, and a few smaller "lumps" in the front of the neck. Drainage of the right frontal sinus was followed by diminution in size of all the "lumps." At about the same date she complained of pains in the region of various joints and of profuse sweating. In 1931 she went West to live, and during an interval of two years there she was aware that the lymph nodes in the back of her neck were still palpable and that they enlarged on "more than a dozen" occasions without obvious cause, only to diminish in size within a short time. In 1933, on incidental palpation of her axillae, she discovered several enlarged nodes on both sides. Each of these nodes was "about the size of an olive." At this time, also, she again began to experience pains in the regions of various joints, both large and small, and finally there was, and still was on examination in July 1936, limitation of motion of the lower jaw and of some of the joints of the fingers. Neither acute swelling nor redness of the joints was noted at any time during the life of the patient.

In July 1936 a physician found a chain of enlarged lymph nodes in the posterior cervical region numbering from six to eight on either side, the individual nodes varying in size from that of a pea to that of a kidney bean. There were also enlarged nodes in both axillae. Shortly thereafter the patient was admitted to the hospital with an acute illness which lasted three weeks and was characterized by fever and profuse sweats, together with so-called rheumatic pains. The nodes in the neck and axillae were found to be slightly enlarged. During her stay in the hospital the nodes diminished in size, but on readmission, three weeks later, the nodes in the axillae and neck had again increased in size, the largest measuring from 3 to 4 cm., and the others from 2 to 3 cm. or less. She was again discharged from the hospital, and in the course of the next three months she suffered at irregular intervals from "arthritis" and "gas pains," accompanied by a temperature of 102 and 103 F., which occasionally rose to 104 F. The white blood cell count was 10,900, with 84 per cent polymorphonuclear neutrophils and 16 per cent lymphocytes. March 16, 1937, she was readmitted to the hospital for the last time, with practically the same symptoms. March 30 she began to show signs of croupous pneumonia of the lower lobe of the left lung. The next day there was some loss of blood through the nose and blood in the stools. April 3 she vomited 1,500 cc. of blood, the temperature ascended to 106 F., and death occurred.

Blood counts were made at various intervals in the years previous to the patient's death, and the white cells averaged 6,000, of which 68 per cent were polymorphonuclear neutrophils. No abnormal forms were found at any time.

At no time was the spleen palpable.

Three agglutination tests for Brucella melitensis infection and one for tularemia were negative, as were persistent attempts to isolate typhoid and paratyphoid bacilli. Malarial parasites were never found. The heterophilic antibody test was negative.

A group of nodes, some of them enlarged to 3 or 4 cm., and others about 1 cm. in diameter, was removed Oct. 22, 1936. A second group of similarly enlarged nodes was removed March 27, 1937, or ten days before the patient's death. All the excised nodes showed essentially the same changes. The architecture showed complete rearrangement of the structure of the node by the interposition of innumerable lymph follicles, some of extraordinary size, others of about normal dimensions, a few that were small and some that were almost completely sclerotic. The better preserved follicles were surrounded by zones of small lymph-

ocytes, closely packed and arranged in rows. The centers of the follicles, which stained rather lightly, were composed partly of large hypochromatic, or shadow, cells and partly of more richly chromatic cells of the large lymphocytic type. The hyperplastic follicles lay in a richly but irregularly vascularized matrix of fibrillar connective tissue which was scattered irregularly throughout the node. This matrix supported a rich sprinkling of small lymphocytes. Among the latter, in places, was to be made out an occasional eosinophil, but in other places eosinophils were herded in large numbers.

Necropsy.—This examination was made three hours post mortem. Externally a solitary enlarged lymph node, 2 by 3 cm. in size, was felt beneath the angle of the left jaw, and a few smaller but easily palpable lymph nodes, 0.5 cm. in diameter, were noted on the opposite side in the same situation. Both axillae revealed several enlarged lymph nodes, measuring 2.5 by 3 and up to 5 cm. and one measuring about 10 cm. in diameter. The inguinal lymph nodes were easily felt and those on the right were larger than those on the left. The anterior mediastinal, mesenteric and retroperitoneal lymph nodes were enlarged in moderate numbers. The right axillary lymph nodes together weighed 125 Gm., and the nodes were discrete. They varied in diameter from 1 to 8 cm. The axillary nodes on the left side weighed 90 Gm., and measured on the average from 3 to 4 cm., the largest among them measuring 6 cm. in its greatest diameter. The nodes in the right inguinal region were moderately enlarged; some of them, however, measured 5 cm. in diameter. A chain of elongated lymph nodes extended along the line of the external iliac and hypogastric vessels, each node measuring from 3 to 4 cm. in length and about 0.5 cm. transversely. The largest among them measured 4 cm. in diameter and was rounded. All the nodes examined were elastic to the touch and succulent in appearance.

The spleen was enlarged, measuring 15 by 9 by 3 cm.; it was firm in consistency and on section revealed uniformly distributed yellowish or somewhat opaque areas, which stood out prominently against the background of the cyanotic parenchyma. For the greater part these areas were rounded and well defined, sometimes showing serrated borders.

The pericardial layers were thickened and adherent to one another. The heart was enlarged and weighed 560 Gm. The muscle was flabby and pale. The valves were normal.

Microscopic Examination.—The normal structure of the lymph node was obliterated—the nodes appeared as if they had been severely shaken or trampled on. The parenchymal remains were represented by a disorderly combination of loosely arranged small lymphocytes containing dense or pyknotic nuclei with even more numerous large, or occasionally very large, jagged or otherwise deformed mononuclear cells having deeply eosinophilic cytoplasm and dense chromatic nuclei of various shapes. Frequently only the cell bodies remained as shapeless masses of granular eosinophilic débris. The lymph follicles were scarcely recognizable as such. They were represented by collections of lymphocytes with ill staining cloudy or pyknotic nuclei, frequently intermingled with the same large deformed eosinophilic cells and the shapeless masses of eosinophilic material already described or by granular débris alone (fig. 2). Follicles so altered were scattered in large numbers throughout the substance of the node and were small, seldom, if ever, attaining large proportions, and were variable in shape. What was left of the connective tissue of the node was represented by reddish staining threadlike fragments. Capillary vessels containing a few red

cells coursed through the broken connective tissue at various angles without any attempt at orderly distribution.

The spleen showed innumerable wrecked and collapsed lymph follicles, consisting individually of one or more small hyalinized arterioles, each of which was surrounded by several layers of thin granular strands of connective tissue and all representing apparently the modified vascular skeletons of originally intact follicles. Other follicular remains consisted of a vascular skeleton with large

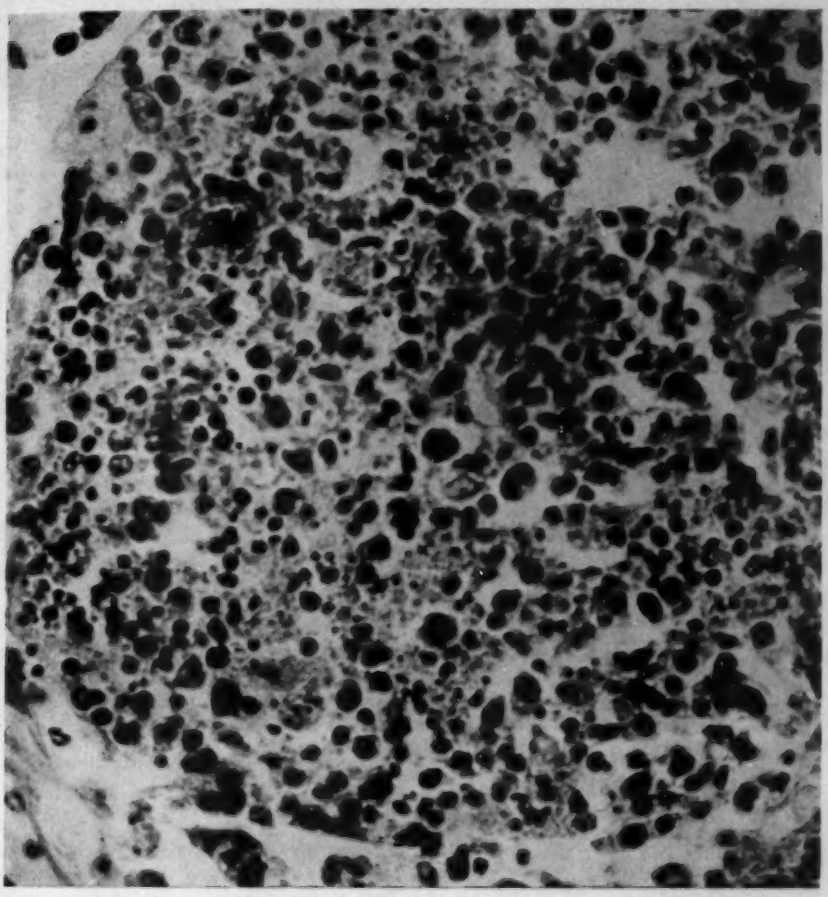

Fig. 2 (part I, case 7).—"Necrotic folliculitis" of lymph nodes and spleen, terminating giant follicular lymphadenopathy of eight years' duration. The picture illustrates necrosis of follicles in lymph nodes.

eccentric collections of necrotic cells and cell débris, the shape of the follicle simulating that of the normal follicle (fig. 3). In still others the vascular skeleton lay in a mass of necrotic cells arranged as irregular islands or streaks, the whole bearing only a recognizable resemblance to the shape of the normal follicle. Wherever found, the necrotic masses were made up of small lymphocytes

with homogeneous cloudy nuclei and of pyknotic nuclei, large mononuclear cells of many different shapes and sizes provided with variously deformed and densely chromatic nuclei as well as with intensely eosinophilic cytoplasm, and amorphous intercellular cytoplasmic and nuclear débris. The degenerative and necrotic changes involved the lymph follicles exclusively.

The rest of the splenic structure showed no noteworthy deviation from the normal except intense congestion of many sinusoids and in other places widespread overgrowth of fibrillar connective tissue, in which there were a few slitlike spaces lined by endothelium and containing an occasional red blood cell.

Fig. 3.—Section from the same case as depicted in figure 2, to illustrate necrosis of lymph follicles in the spleen.

The outer and inner layers of the pericardium were thick and composed almost exclusively of collagenous fibrils. Between these layers was a thick layer of fibrillar connective tissue intermingled with collagenous fibrils, embedded in which were numerous small, thin vessels, a few histiocytes and an occasional eosinophil. The walls of a few of the blood vessels were thickened and hyalinized.

The heart muscle appeared to be well preserved.

Comment.—The capricious clinical behavior of enlarged lymph nodes over a period of nine years, the fever, profuse sweating, pains in joints and fixation of joints, the hyperplastic follicular changes observed in the lymph nodes during life and the necrotic follicular changes observed in the lymph nodes and spleen after death, together with the adherent pericardium, form the outstanding features of a disease which is believed to be unique.

SUMMARY

According to the observations recorded in this paper, giant follicular lymphadenopathy is characterized clinically by local or generalized enlargement of the superficial nodes and, in about 64 per cent of the cases synopsized or described, by splenomegaly. In certain instances the deeper nodes are enlarged, either alone or in combination with the superficial nodes. The individual nodes vary in size from 1 to 5 cm. or more, are almost always discrete and movable, but may be so closely packed, especially in the inguinal region, as to appear confluent. As a rule they are rounded or oval, painless and not tender. Usually they are firm in consistence, although occasionally they are rather soft and may even break, discharge a thin watery or faintly cloudy fluid and heal slowly. Sometimes individual nodes or small groups of nodes may diminish in size spontaneously or disappear for a while. Spontaneous attempts at healing may occur, as shown histologically by patches of granulation tissue, interfollicular connective tissue overgrowth and sclerotic follicles.

Enlargement of the nodes is due to numerical and dimensional hyperplasia of the lymph follicles. Lymph cords and sinuses are practically always obliterated. Almost every follicle is delimited by a zone of closely set, deeply staining small lymphocytes, laid down in one or more rows arranged in orderly sequence and fading gradually into the loosely distributed small lymphocytes of the parenchyma. The germinal areas vary in their staining qualities. Some of them stain lightly, and these are composed mostly of the large embryonal follicular cells which are so poor in chromatin as to appear as shadow forms. Others stain more deeply, being composed of the smaller embryonal follicular cells of the large lymphocytic type, the nuclei of which are relatively rich in chromatin. In the greater number of follicles there is an admixture of the two main varieties, and transitional forms may enter into the histologic picture in variable numbers. The latter are about midway in size between the two main varieties and are often indented or otherwise apparently deformed; they contain chromatin noticeably in excess of that of the large shadow-like hypochromatic cells and are traceable into the comparatively richly chromatic rounded or oval cells of the large lymphocytic type.

The lymph follicles differ in size and shape. Many of them are massive; others are enlarged in varying proportions; still others are diminutive. For the greater part, the follicles are rounded or oval, but in numerous instances they are fused to form enormous masses of different shapes, or the individual follicles may assume a variety of forms—clover leaf, kidney, boat, hook or beak shaped, sometimes with, and at other times without, breaks in the containing wall of small

lymphocytes. They may be so closely packed as to occupy almost all of the substance of the node, or they may be set apart at variable distances, the intervening areas consisting of small lymphocytes.

Splenomegaly is likewise due to hyperplasia of lymph follicles. Clinically, the enlargement may vary in size from one which is barely palpable to one which assumes enormous proportions.

In the earlier stages the leukocyte count is apt to be normal. After the lapse of a year or more leukopenia is often encountered, and in the differential count polymorphonuclear eosinophils may be noted oftener than in the average patient, or even a mild degree of eosinophilia may occur.

Giant follicular lymphadenopathy with or without splenomegaly is unique and easily identifiable. It is probably of "inflammatory" or "toxic" origin and is usually amenable to mild roentgen therapy.

II. TRANSFORMATION OF GIANT FOLLICULAR LYMPHADENOPATHY INTO POLYMORPHOUS CELL SARCOMA OF THE LYMPH FOLLICLES

CASE 1.—A white man aged 22, employed as a shipping clerk, was admitted to Bellevue Hospital Aug. 16 and was discharged Sept. 26, 1937, a patient of Drs. Charles Nammack and S. B. Ross. He complained chiefly of swollen and painful nodes in the neck, which had been present since May. There was nothing of interest in the past history except that he was admitted to Bellevue Hospital in April with generalized edema, bloody urine and vomiting, following an acute infection of the upper part of the respiratory tract. At that time, it was suspected that he suffered from acute glomerular nephritis. He improved to such an extent that all of these symptoms disappeared and the urine was normal by August.

The first enlargement of a node to appear was in the left posterior auricular region. This was followed three weeks later by another enlargement in the superior cervical region on the right side and later by the appearance of a discrete axillary mass on the right side and enlargement of the inguinal nodes on the left. All of the enlarged cervical nodes were tender. Early in September there was, in addition, a large oval or egg-shaped movable mass, nontender, lying near the angle of the jaw on the right side. It measured about 5 by 2.5 by 2 cm. In the immediate vicinity were about one-half dozen enlarged nodes, varying in diameter from 1 to 2 or 3 cm., discrete, movable and nontender. A few moderately enlarged nodes were met with in the right side of the neck. August 24 a slightly enlarged submaxillary lymph node was removed from the right side.

The red blood cell count was 5,840,000; the hemoglobin content, 70 per cent; the leukocyte count, 11,450, with polymorphonuclears 80 per cent and lymphocytes 20 per cent.

Microscopic examination of the excised node revealed obliteration of the normal architecture and partial replacement by enlarged round or oval follicles. Each of the better preserved follicles was delimited by a narrow zone of well preserved small lymphocytes. Immediately adjacent was a broad zone made up of larger rounded cells with relatively lightly staining nuclei, the cells corresponding apparently to well preserved large lymphocytes. In many instances the latter cells were heaped to form moundlike elevations at some part of the follicular

boundary. The germinal areas were composed for the greater part of large hypochromatic shadow cells, intermingled with transitional forms and hyperchromatic cells of the large lymphocytic type. An occasional ruptured follicle was to be seen, its cell content projecting into the substance of the node. The interfollicular areas showed vast numbers of diffusely distributed large hypochromatic shadow forms, a few transitional cells and a rich sprinkling or an occasional island of hyperchromatic cells of the large lymphocytic type.

No reticulum cells were revealed by silver impregnation. Reticulum fibers were numerous but were rarely found in the follicles.

CASE 2.—A man aged 29 was referred from the Hospital for the Ruptured and Crippled through Drs. Norman Higinbotham and D. A. DeSanto. On April 17, 1937, he sustained a fracture of the left clavicle while playing ball. He was admitted to the Hospital for the Ruptured and Crippled. After the fracture had apparently healed, a mass appeared near the medial end of the clavicle on the anterior surface. The mass was not painful or tender. It was learned of him that in June 1936 he had been seen in the outpatient department and had complained of numbness in the region of the left clavicle. Roentgen examination at that time suggested Brodie's abscess. When he was seen in April 1937, a punch specimen obtained for biopsy showed red blood cells, polymorphonuclear leukocytes and fragments of fibrous tissue.

June 24 roentgen examination showed in the middle third of the medullary canal of the left clavicle a cystlike rarefaction, about 1.5 cm. in diameter, which was sharply defined and was thought to be a tumor or a Brodie abscess. July 7 roentgen examination showed that the mass was larger and that it had a multilocular or honeycombed appearance.

The patient insisted that he had had enlargement of the lymph nodes of the cervical, axillary, epitrochlear and inguinal regions for a period of two years before the fracture, which occurred April 17, 1937. In June 1936 physical examination revealed palpable enlargement of the spleen. The lymph nodes of the cervical, axillary and inguinal regions were large, firm and discrete, measuring from 2.5 to 5 cm. in diameter. The laboratory studies showed nothing worthy of interest except leukopenia, the white cell count being 5,400.

July 9, 1937, that is to say, approximately three years after the onset of lymph node enlargements and splenomegaly, a lymph node was removed from the right axilla. Microscopic examination showed practically complete replacement of the node by hyperplastic lymph follicles, many of which were of massive size. For the greater part, the follicles were irregularly rounded, some were fused, others appeared as large cellular islands with no attempt at orderly configuration. Those follicles which appeared to be relatively intact lay in a matrix of diffusely distributed, richly chromatic cells of the large lymphocytic type. A few small lymphocytes were identified among these. In numerous instances the follicles were composed almost exclusively of large hypochromatic, or shadow, cells; others revealed a more or less rich admixture of hyperchromatic cells of the large lymphocytic type, among which transitional forms were frequent; still others showed a variable mixture of the three types of cells (fig. 4). The same cell picture presented itself throughout those parts of the node that had become inundated by the cellular elements from partly or completely ruptured follicles. Special stains for reticulum cells were negative.

September 22 the following note was made: "Under roentgen therapy all the nodes have diminished noticeably in size but are still easily palpable, and there seems to be a slight decrease in the size of the mass in the clavicle."

CASE 3.—A 26 year old colored man, a prize fighter, was admitted to Bellevue Hospital July 26 and was discharged Aug. 15, 1937, from the Second Medical Division (acting director, Dr. A. L. Lincoln). He stated that about a month before admission while working in a cold storage room in a restaurant, he "caught old," after which he began to experience pains in various parts of the body, including the shoulders, the right thigh and the right knee. At no time was there redness or swelling. On admission it was found that there was

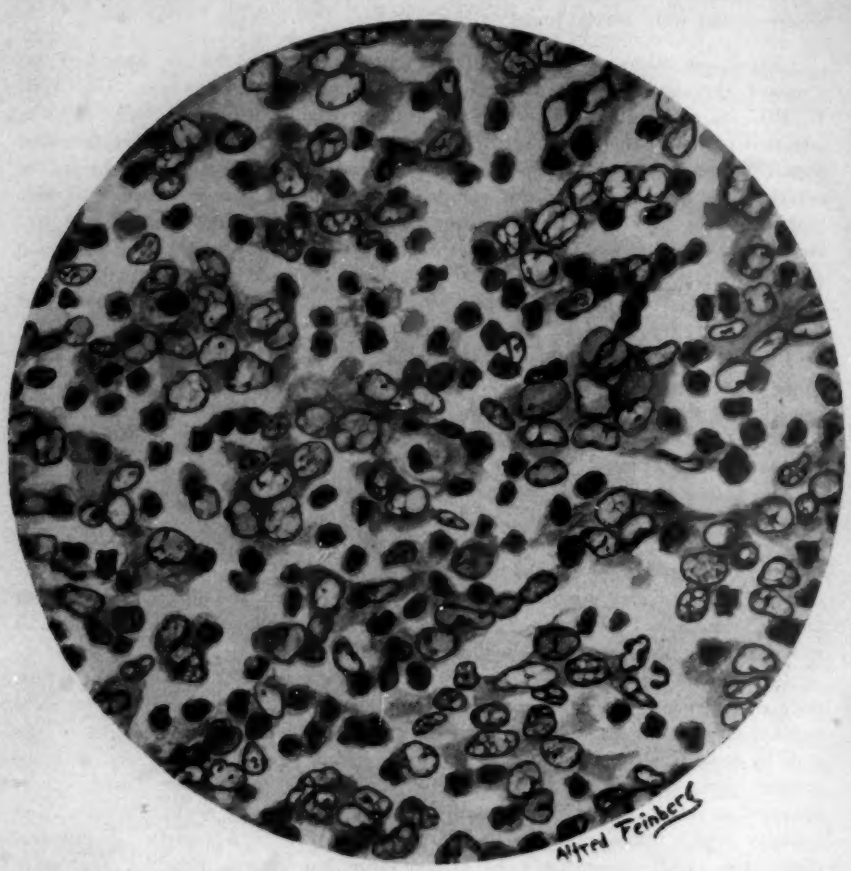

Fig. 4 (part II, case 2).—Drawing to illustrate cell types in the polymorphous cell sarcoma following neoplasmic transformation of giant follicular lymphadenopathy: large hypochromatic, or shadow, cells; smaller, slightly chromatic transitional cells, and hyperchromatic cells of the large lymphocytic type. Oil immersion lens.

generalized enlargement of the lymph nodes, including those in the anterior and posterior cervical regions, the axillae and the inguinal and femoral regions. The nodes varied from 1 to 3 cm. in diameter, and were rounded or oval, firm in consistence, freely movable and not tender. The spleen and liver were not palpably

enlarged. Physical examination revealed nothing further worthy of note except for a well healed, smooth cuplike scar at the external penile meatus. The Wassermann reaction was 4 plus. The blood count was essentially normal; the leukocyte count varied from 7,100 to 9,050.

Two enlarged lymph nodes were removed from the neck. Microscopic examination showed numbers of hyperplastic lymph follicles, many of which were circumscribed by small lymphocytes. Ruptured follicles were present in considerable numbers. In some sections the germinal centers were made up almost exclusively of large hyperchromatic cells of the large lymphocytic type; in other sections they were composed practically exclusively of large hypochromatic, shadowlike cells. The parenchyma of the node showed innumerable cells of the latter type arranged in islands or diffusely. In still other places hyperchromatic cells of the large lymphocytic type were diffused through the substance of the node. No mitoses were observed. Reticulum cells were not demonstrable by silver impregnation.

Comment.—Of the 32 cases of giant follicular lymphadenopathy with its derivative and associate lesions synopsized or described in this paper, this is the only instance in which the presence of syphilis was determined.

Case 4.—A colored man aged 40, a native of Portugual, was admitted to Bellevue Hospital Jan. 29, 1937, in the service of Dr. Howard Fox. He complained of gradual darkening of the skin of one year's duration. At the time of admission the skin of the entire body was jet black, markedly thickened and thrown into rugae resembling corduroy. There were no signs of desquamation. At scattered intervals were rounded or streaklike areas in which the skin was almost dead white and smooth. The skin of the palms and soles was moderately thickened, roughened and brownish, with scattered whitish areas. In addition, there were innumerable enlarged firm discrete lymph nodes in the neck, supraclavicular, axillary, inguinal, subinguinal and popliteal regions, the individual nodes varying in size from 1 to 4 cm. and numbering, in their respective situations, from one or two to fifteen or twenty. Of these the patient was unaware until they were pointed out to him after his admission to Bellevue Hospital. He was otherwise in good health. The spleen was not palpable, and the blood counts were normal.

Microscopic examination of the skin showed nothing of interest in the present connection except large quantities of yellowish brown pigment in the lowermost epithelial layers and in the subepithelial connective tissues.

Microscopic examination of an excised lymph node showed marked numerical and dimensional hyperplasia of the lymph follicles. Most of the follicles were rounded or oval; some were elongated or dumbbell shaped; they were delimited partly or completely by richly chromatic rounded cells larger than small lymphocytes. The germinal areas were composed of large hypochromatic, or shadow, cells and hyperchromatic embryonal cells of the large lymphocytic type in approximately equal numbers. In the substance of the node, and largely replacing it, were vast numbers of cells of an essentially identical sort, either arranged in the form of massive, disrupted follicles or scattered diffusely without any attempt at preservation of follicular form. No mitotic figures were observed. Lying free throughout the node were countless deposits of yellowish brown pigment. Silver impregnation for reticulum cells showed none.

A prolonged course of roentgen therapy resulted in no appreciable diminution in the size of the enlarged nodes, and the skin lesion remained unchanged.

CASE 5.—A man aged 42, white, was admitted to Bellevue Hospital Feb. 17, 1937, in the service of Dr. Howard Fox. He complained of an incapacitating skin disorder of nine years' duration, for which he had received various forms of treatment without other than temporary relief. The entire body was involved. The skin was brownish black and was covered by rounded vesicles containing a thin, watery fluid. The vesicles seldom exceeded 1 cm. in diameter before rupture. This usually occurred at one arc, leaving a semilunar rim of fluid and a moist base covered by whitish, macerated epithelium. From this point the ruptured vesicles progressed to form sheets of dry, desquamating epithelium varying in size from that of the original vesicle to the familar "pie crust" exfoliations. There was no complaint of itching.

A few days after the patient's admission solitary enlarged lymph nodes were detected in both supraclavicular spaces, the nodes being discrete, rounded and firm, measuring about 1 cm. in diameter. Clusters of eight or ten similarly enlarged nodes, each node measuring between 1 and 4 cm. in diameter, were present in both axillae, and the inguinal and subinguinal nodes were enlarged to the number of twenty or more, each node measuring between 2 and 4 cm. Until his entrance into Bellevue Hospital the patient was not aware of the existence of the enlarged nodes. The blood counts showed nothing of note in the present connection.

Microscopic examination of an excised lymph node revealed numerical and dimensional hyperplasia of the lymph follicles, many of which were completely surrounded by thick mantlings of richly chromatic rounded cells. At the periphery these cells, in many of the follicles, were distinctly larger than small lymphocytes and, as one approached the centers of the follicles, they became still larger, often assuming indented forms, and their nuclear chromatin became stippled, angulated or otherwise distorted. The centers of the follicles stained lightly and were composed of great numbers of relatively very large hypochromatic, shadow-like cells, intermingled with transitional cells and cells of the large lymphocytic type just described. Ruptured follicles were numerous, and the substance of the node showed an extensive admixture of cells essentially identical with those just referred to. No mitotic figures were observed. Among the cells throughout the node were numerous deposits of brownish yellow amorphous pigment. Silver impregnation for reticulum cells showed none.

A prolonged course of roentgen therapy resulted in complete disappearance of the enlargement of the nodes (December 1937), but this reappeared in June 1938.

Comment.—In certain cases there appears to be a relationship between generalized chronic pigmentary disorders of the skin, especially dermatitis exfoliativa, and local or generalized enlargement of the superficial lymph nodes. At Bellevue Hospital there have been encountered at necropsies, including four performed under the auspices of the Office of the Chief Medical Examiner, 17 cases of dermatitis exfoliativa associated with poisoning by arsphenamine. In 2 of the cases the histologic nature of the superficial generalized lymphadenopathy was not determined. Among the remaining 13 were 3 cases of Hodgkin's disease, 1 of extensive tuberculous lymphadenopathy and 2 of polymorphous cell sarcoma of the follicles of lymph nodes. The latter 2 cases are recorded in this paper. The remaining cases showed nothing of interest in the present connection.

The question of priority of origin naturally arises. In most cases that I have encountered at necropsy or clinically the superficial lymph nodes were of such relatively small size as to suggest that the lesions of the skin preceded the changes in the lymph nodes. In at least 2 instances the patients were unconscious

of the generalized enlargement of the lymph nodes. On the other hand, in one of the cases at Bellevue Hospital the patient presented what was histologically proved to be widespread tuberculous lymphadenitis in the neck, axilla and groin over a period of three and a half years preceding the onset of dermatitis exfoliativa—a feature which may be interpreted as causative or incidental, as one pleases.

CASE 6.—A colored man aged 30 entered Bellevue Hospital May 24, 1937. He complained of a painful lump in the left side of the neck of six months' duration. Physical examination revealed in the left side of the neck an oval mass, measuring 4 cm. in diameter, firm, discrete and not tender. In the right side of the neck there was a chain of about four moderately enlarged nodes lying beneath and behind the sternocleidomastoid muscle, the largest node measuring about 2 cm. in diameter. No enlarged nodes were detected in any other part of the body, and the spleen was not palpated.

Roentgen treatment was started May 24 and was given to both sides of the neck in doses of 2,250 roentgens at intervals of from three to four days. September 23 the course of treatment was completed, the nodes showing no favorable response. A rest period of six weeks followed. November 6 another course of roentgen therapy was started, in which the quality of the ray was changed by increasing the filter. Both sides of the neck were treated daily with 1,800 roentgens. The course was finished November 22. At that time the nodes on both sides of the neck were larger than at the outset of treatment.

Early in May 1937 a cervical node was removed, and microscopic examination showed replacement of its architecture, due partly to moderate numbers of hyperplastic lymph follicles, the germinal areas of which were made up of large hypochromatic, or shadow, cells with a fair admixture of transitional forms and a few hyperchromatic cells of the large lymphocytic type. Elsewhere the node revealed great numbers of large hypochromatic cells arranged as large rounded or oval islands or in streaklike formations, sometimes communicating one with the other in plexiform fashion or assuming irregularly globular or sausage-like shapes. Hyperchromatic cells of the large lymphocytic type stood out in sharp contrast because of their richer content of chromatin. No mitotic figures were observed. Silver impregnation revealed no reticulum cells. Reticulum fibers were abundant.

Comment.—The case just described is an example of localized giant follicular lymphadenopathy undergoing transformation into polymorphous cell sarcoma of the germinal areas. The growth was radioresistant.

CASE 7.—A man aged 50, a bread salesman, was admitted to Manhattan General Hospital Aug. 31 and was discharged Sept. 16, 1936. He was a patient of Dr. Joseph Bodansky, referred by Dr. A. M. Sala. This patient complained of a swelling in the right groin. Physical examination revealed a mass "about the size of a lime," firm, slightly irregular, lying below Poupart's ligament. It was removed by operation. The mass measured 6 by 4.5 by 2.5 cm. and was grayish white, rather firm and elastic. No other masses were found.

Microscopic examination of the excised tissue showed innumerable massive lymph follicles, some of which were completely surrounded by rows of small lymphocytes (fig. 5). Many of the great follicles were ruptured. The germinal areas consisted rather preponderantly of hyperchromatic cells of the large lymphocytic type with an admixture of large hypochromatic, or shadow, cells and transitional forms. Ruptured follicles were associated with vast numbers of cells

of the same type infiltrating and replacing the body of the node (fig. 6). No mitotic figures were detected. Silver impregnation failed to reveal reticulum cells.

After leaving the hospital the patient received roentgen therapy. Nov. 20, 1937, I saw the patient at the French Hospital, New York, in consultation with Dr. Arthur M. Wright, and neither of us could detect any enlargement of lymph nodes or signs of splenomegaly.

Comment.—This case just presented emphasizes the fact that giant follicular lymphadenopathy may originate in a localized group of nodes and undergo sarcomatous transformation.

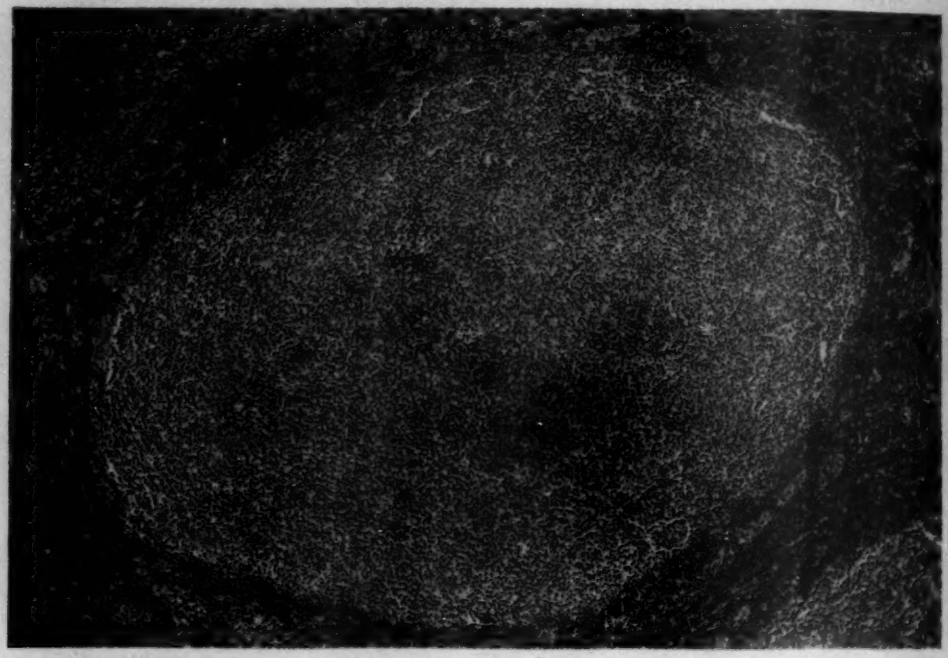

Fig. 5 (part II, case 7).—Low power photomicrograph to illustrate giant follicular lymphadenopathy as a precursor of polymorphous cell sarcoma of lymph nodes. Note intact follicle. See figure 6.

SUMMARY

A polymorphous cell tumor of lymph nodes is described in the series of cases just presented. It is believed to represent sarcomatous transformation of the follicles in giant follicular lymphadenopathy.

On morphologic grounds it may be assumed that the polymorphous cell sarcoma of lymph follicles is composed of immature lymphocytes in view of the fact that its massive hypochromatic cells are traceable through smaller transitional cells, slightly richer in chromatin, into still smaller but richly chromatic cells which bear an arresting resemblance to large lymphocytes and that all of them are derived from follicles

which are set aside, at least partly, for the purpose of producing lymphocytes. If one prefers to argue in the opposite direction and to assume that the hyperchromatic cells of the large lymphocytic type regress into the proportionately massive hypochromatic cells of shadow type through transitional forms, the fact remains that the cell content of the tumor is unchanged. No matter what the sequence of events may

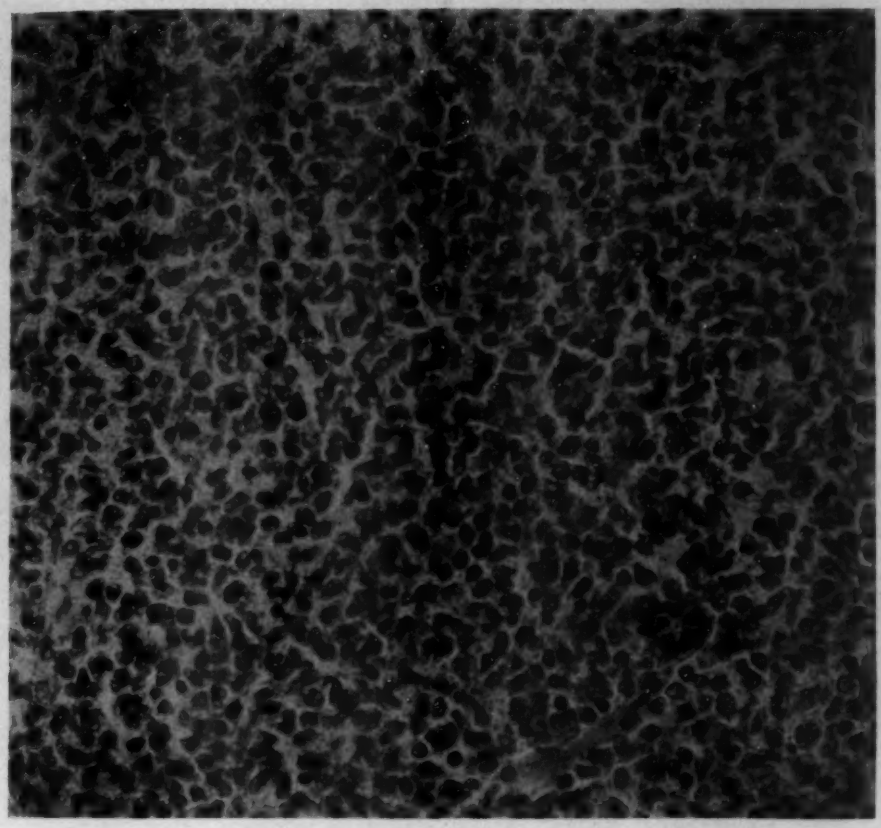

Fig. 6.—High power photomicrograph taken from a ruptured follicle in the case depicted in figure 5, to illustrate polymorphous cell sarcomatous transformation of giant follicular lymphadenopathy. It shows infiltration of the body of the node by hordes of large hypochromatic, or shadow, cells and smaller hyperchromatic cells of the large lymphocytic type.

be, either in the evolution or in the descent of the cells, it appears to be probable that these cells are immature lymphocytes showing histologic variations. A tumor made up of these cells might therefore be appropriately designated a polymorphous cell lymphosarcoma. However, in view of the uncertainties involved I think it would be wise to

adopt the noncommital designation of polymorphous cell sarcoma rather than to bind oneself to the diagnosis of lymphosarcoma until there is conclusive evidence that the unit of growth is a lymphocyte, no matter how enticing the probability may appear to be. That the unit of growth is not a reticulum cell seems to be established, if the method of investigating reticulum and reticulum cells by the process of silver impregnation is to be relied on.

For example, even at the risk of repetition, it may be mentioned that in the polymorphous cell sarcoma originating on the basis of regional or generalized giant follicular lymphadenopathy the lymph follicles remain numerically and dimensionally increased, the hyperplastic follicles rupture, and three morphologically distinct cells infiltrate the substance of the nodes—the very large hypochromatic, or shadow, cells, the smaller hyperchromatic cells of the large lymphocytic type and the poorly chromatic transitional cells. None of these cells is traceable to the reticulum apparatus of the node—none is provided with fibrillae stainable by special reticulum cell stains, although supporting reticulum fibers may be present in the follicles and, in greater or less numbers, in other parts of the node. If reticulum cells are derived from fibroblasts, the so-called reticulum cell lymphosarcoma is not a lymphosarcoma, because the unit of growth is not a member of the hemopoietic series. If reticulum cells are derived from lining endothelium, such as that of the sinuses of the lymph nodes, then again the so-called reticulum cell lymphosarcoma is not a lymphosarcoma but a reticuloendothelioma. It is evident that the existence of the so-called reticulum cell lymphosarcoma has been hypothecated on premises which are not tenable or, in other words, that the conception of a lymphosarcoma composed of reticulum cells is unsound. On the other hand, there is a universally recognized variety of tumor of lymph nodes known as large round cell sarcoma. It is not derived from or associated with hyperplasia of the lymph follicles, either dimensional or numerical. In many quarters the designation "large round cell sarcoma" is used synonymously with "reticulum cell lymphosarcoma." "Large round cell sarcoma" is a legitimate descriptive term. The unit of growth is usually assumed to be a large lymphocyte. In my opinion the term "reticulum cell lymphosarcoma" should be abandoned as misleading in that such a tumor has not been shown to occur. I draw particular attention to this phase of the subject in order that the large round cell sarcoma of lymph nodes may not be confused with the polymorphous cell sarcoma of lymph follicles described in this paper.

It is to be noted as a matter of no small importance in the histogenesis of the polymorphous cell sarcoma of lymph follicles that mitoses are conspicuously absent.

Finally, it is a matter of clinical concern that the polymorphous cell sarcoma of lymph follicles is radioresistant in a certain percentage of cases, although radiation therapy in some instances may be followed by temporary reduction in the size of the enlarged nodes or even by disappearance of the condition. The large round cell sarcoma of lymph nodes is radiosensitive.

III. ASSOCIATION OF GIANT FOLLICULAR LYMPHADENOPATHY WITH HODGKIN'S DISEASE

CASE 1.—A man aged 34, a mechanic, was admitted to Bellevue Hospital Oct. 23 and was discharged Nov. 25, 1930, from the Fourth Medical Division (director, Dr. Charles Nammack). He was referred by Dr. Harry Solomon. He died Sept. 23, 1934.

The patient stated that he had been troubled with his nose and throat since childhood. Both tonsils were removed when he was 7 and a submucous operation was performed when he was 16. Up to that time (1912) no enlargement of lymph nodes had been noted in any part of his body. Thirteen years later in May 1925 he noticed that his neck was growing larger. Until that time he had been accustomed to wear a 15½ size shirt. In the course of the next three years he was forced to wear size 16, 16½, 17, 17½ and 18, and finally the latter size would not go around his neck. In July 1927 he had an operation on the left maxillary antrum, the antrum being drained through the nose. At the time of operation there were innumerable discrete masses in the neck and moderate numbers scattered through the axillae and groins. In May 1928 he submitted to another operation for drainage of the antrum on the same side. Six months later he was again enabled to wear a 15½ size shirt. He stated that after the operation in 1928, as long as the antrum drained adequately the nodes remained diminished in size but that recently the opening had "clogged up," with the result that the nodes had returned to their former size. Another operation was performed for drainage of the same antrum, after which the nodes in the neck rapidly diminished to such an extent that the patient was again able to wear a 15½ size shirt (February 1931).

In October 1930 the red blood cell count was 5,100,000 and the hemoglobin content was 85 per cent. The white cell count was 13,200, with polymorphonuclears 64 per cent, lymphocytes 34 per cent and eosinophils 2 per cent.

On the patient's admission to Bellevue Hospital in 1930 there were considerable numbers of enlarged lymph nodes discrete, rather soft and painless, scattered through the neck both anteriorly and posteriorly. The axillary nodes were enlarged to the number of about four, those on the right side aggregating "the size of a large walnut," those on the left, "the size of one's thumb nail." Palpably enlarged deep inguinal nodes were encountered to the number of three or more on each side. The spleen was palpable 2 fingerbreadths below the costal slope on the left side. The liver was palpable 5 fingerbreadths below the right costal slope.

Early in November 1930 one of the enlarged cervical nodes was removed. It revealed marked dimensional and numerical hyperplasia of the lymph follicles. The follicles stood out as lightly staining bodies, round or oval, sometimes fused; each was partially, occasionally completely, surrounded by a zone of small lymphocytes and was composed largely of hyperchomatic cells of the large lymphocytic type. The interfollicular cells were small lymphocytes.

In 1931 the patient was admitted to the clinic of Dr. Lloyd F. Craver,[5] at the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, at which time the patient presented generalized lymphadenopathy. Dr. Craver stated that " . . . frequently throughout the subsequent course of three years and four months the blood count suggested a low-grade lymphatic leukemia, although at other times the differential count was fairly normal. At one time, for example, a count of 8,000 white cells was obtained, with 83 per cent small lymphocytes, and counts of about 6,000 white cells with 50 to 60 per cent small lymphocytes were frequent."

Nov. 23, 1933, the patient was readmitted to Bellevue Hospital with moderate but generalized enlargement of the lymph nodes of three weeks' duration. He said that in the intervening three years he had suffered no particular inconvenience from this source. In addition to the enlarged superficial nodes, nodular masses were palpated in the retroperitoneal region below the lower level of the liver and spleen. The spleen was palpated 2 fingerbreadths below the left costal margin, and the liver reached to the level of the umbilicus.

During the patient's second stay in the hospital he was given a series of twelve injections of a mixture of erysipelas and prodigiosus toxins (Coley) without appreciable effect on the enlarged lymph nodes and spleen. Up to this time, in the eight years and six months of his illness the patient had not received roentgen treatment, and, according to the records at Bellevue Hospital, attention had been focused primarily on treatment of the infected antrum.

In 1933 the red cell count was 4,600,000 and the hemoglobin content 90 per cent. The white cell count was 7,500. The differential count showed: polymorphonuclears, 61 per cent; transitionals, 3 per cent; lymphocytes, 35 per cent; eosinophils, 1 per cent.

The patient died and his body was subjected to necropsy at the Memorial Hospital Sept. 23, 1934.

Necropsy.—Dr. Craver sent me a copy of the necropsy protocol and microscopic preparations of lymph nodes, liver, spleen and kidney. My synopsis of the necropsy protocol follows:

There was slight pitting edema of both legs, most marked in the pretibial areas but extending to the iliac crests. The lymph nodes in the neck, axillae and groins were enlarged, none of them exceeding 1.5 cm. in diameter. The trachea was displaced to the left and backward, and both large bronchi were constricted to the extent of about 1 cm. by a massive group of confluent nodes, measuring about 6 by 8 by 8 cm. The thoracic aorta and the innominate vessels were submerged in pinkish white, rather firm tissue, which was continuous with similar tissue in the anterior mediastinum, passing to the posterior mediastinum through the hilar region of the lungs. The abdomen revealed a tremendous sheetlike growth of grayish pink homogeneous tissue in the preaortic area, extending from the diaphragm to the hollow of the sacrum. It was about 9 cm. in thickness and filled the mesentery. Some celiac nodes were present and measured 8 by 6 by 6 cm. The liver showed diffuse nodular involvement, some of the nodules measuring 8 cm. in diameter. The spleen weighed 1½ pounds (680 Gm.) and showed to the naked eye no indication of involvement.

The abdomen contained about 3,000 cc. of clear straw-colored fluid, the pleural cavities over 1,000 cc. and the pericardium 250 cc.

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5. Craver, L. F.: Am. J. Cancer **26**:124, 1936.

Microscopic Examination.—I examined the several microscopic sections of lymph nodes sent to me by Dr. Craver. The lymph nodes showed various changes. Some of them were still to be identified as lymph nodes; they showed the presence of numerous skeleton lymph follicles; the lymph cords were rearranged but were still recognizable as such, and were packed with small lymphocytes, and the lymph sinuses were still recognizable. In other nodes, however, the architecture was markedly changed and, in addition to a profusion of large mononuclear cells, there were numerous giant cells of the megakaryocytic type. The substance of the kidney was extensively replaced by innumerable, fairly closely packed cells of the large lymphocytic type, mononuclear giant cells and numerous giant cells of the megakaryocytic variety.

Microscopic examination of the spleen failed to reveal any changes which could be interpreted as those of Hodgkin's disease. The liver, in the sections sent to me, showed nothing of interest in the present connection.

My diagnosis, based on the necropsy report and the histologic observations, is in accord with that made at the Memorial Hospital, namely, Hodgkin's disease.

Duration of Illness.—The patient's illness from the onset of the enlargement of lymph nodes to death occupied a period of nine years and four months.

Case 2.—A groceryman aged 39 was admitted to Bellevue Hospital, the Third Surgical Division, March 16 and was discharged March 20, 1936. He was referred later by Dr. A. M. Sala, pathologist, New York City Cancer Institute. He died Oct. 15, 1937.

The patient entered the hospital because of a large mass in the left axilla that was causing local pain. He stated that about six months before admission he was advised to have the mass removed but refused to do so. The mass grew larger and at the time of admission it measured 11 cm. in diameter and was firm, not tender and freely movable. A few days after his discharge, he was admitted to the Park West Hospital, and the mass in the axilla was removed by Dr. Robert P. Wadhams. April 8, 1936, the patient was referred to the New York City Cancer Institute, where he was given a course of roentgen therapy directed to the left axilla. August 19 a mass "about the size of a hazelnut" was removed from the left axilla. September 21 a solitary enlarged lymph node was noted behind the lobule of the left ear, and a firm enlarged node near the tip of the mastoid on the same side. In both sides of the neck were masses of enlarged lymph nodes, each mass measuring about 2.5 cm. in diameter, and in the posterior part of the neck on the left side were a few discrete movable nodes. The spleen was not palpable at any time during the patient's illness.

I examined microscopically a lymph node removed at the Park West Hospital about April 1, a section of which was sent to me by Dr. J. B. Pinkus. This showed complete obliteration of the normal markings and replacement by a delicate and irregularly distributed matrix consisting for the greater part of a structureless pinkish material, embedded in which were numbers of scattered lymphocytes, giant cells of the megakaryocytic type in moderate numbers, innumerable eosinophils, arranged partly diffusely and partly in islands (fig. 7). In other places the framework was plentiful and consisted partly of irregularly distributed thin strands of apparently mature connective tissue. In both places the supporting tissues revealed noticeable but not conspicuous members of large hypochromatic cells of the shadow type.

A portion of the lymph node removed at the New York Cancer Institute August 19, was given to me for microscopic examination. The surface was partially

covered by skin, which in one place was ulcerated. Microscopic sections of the lymph node were cut in the usual routine fashion from the same paraffin block, and the stained sections revealed a series of rather startling histologic changes. In the first sections to be cut, enlarged lymph follicles were found in large numbers. They varied in shape and size (fig. 8). Some of them were defined by small lymphocytes; others were ruptured. The germinal areas consisted of large hypochromatic cells with a liberal sprinkling of hyperchromatic cells of the large lymphocytic type. A second series of sections cut from the same paraffin block

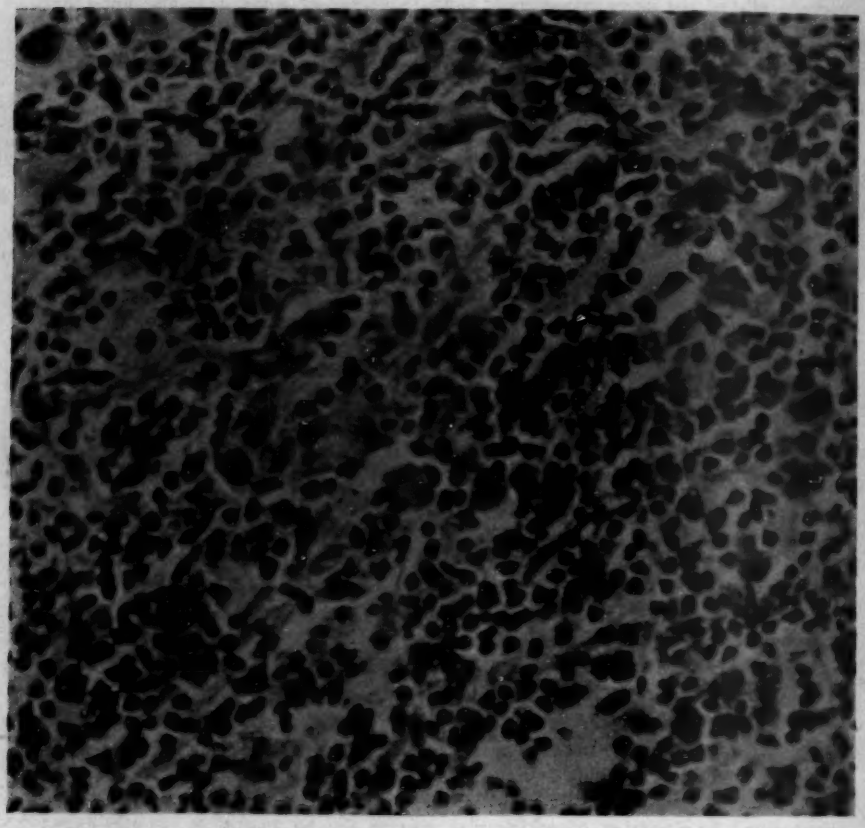

Fig. 7 (part III, case 2).—Section from first biopsy specimen, illustrating the histologic picture of Hodgkin's disease.

revealed a stroma made up practically completely of pinkish staining, finely granular material, embedded in which were great numbers of large hypochromatic, or shadow, cells, a sprinkling of hyperchromatic cells of the large lymphocytic type, many plump spindle-shaped cells, poorly chromatic, resembling fibroblasts, and an occasional giant cell of the megakaryocytic variety (fig. 9). In a third set of sections cut from the same paraffin block, the histologic picture showed delicate bands of fibroblastic connective tissue arranged at a distance from but

Fig. 8 (part III, case 2).—Section from second biopsy specimen, illustrating hyperplastic lymph follicles.

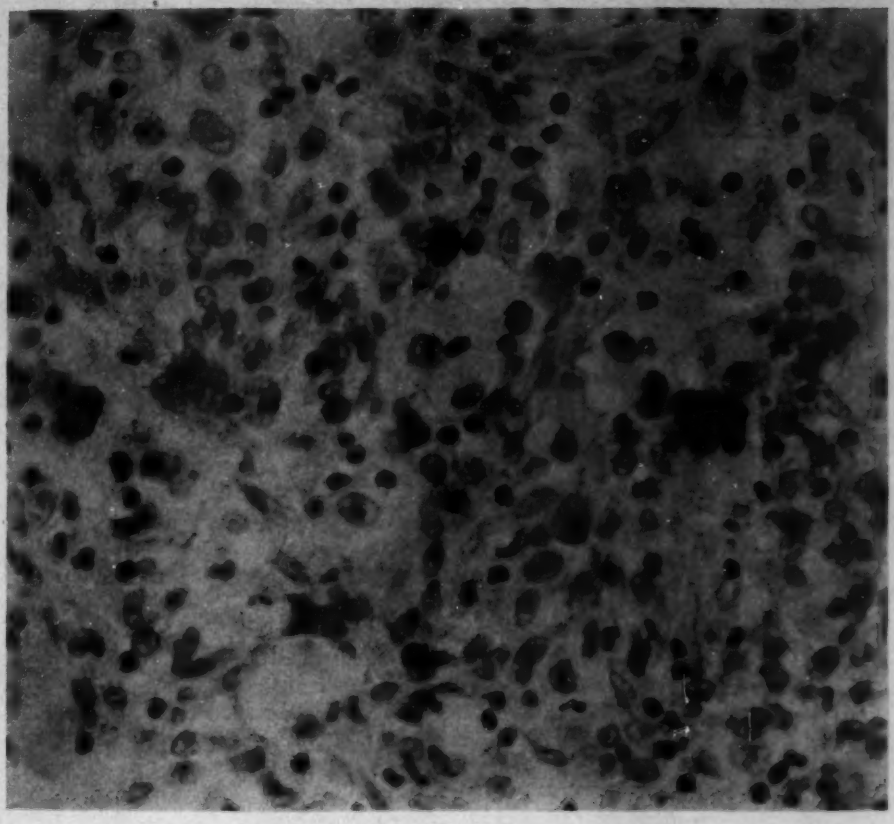

Fig. 9 (part III, case 2).—Section from the same paraffin block as the section in figure 8, illustrating the histologic picture of Hodgkin's disease.

often parallel with one another. The interstices were occupied by myriads of large, plump, rounded, oval or elongated nuclei, the chromatic content of which varied from a few scattered granules to dense, deeply staining masses, apparently representing immature fibroblasts. In many instances these nuclei were massed or even fused to form giant nuclei of many peculiar shapes (fig. 10). After diligent search of different sections a few giant cells of the megakaryocytic type were found. Large hypochromatic nuclei, indistinguishable morphologically from those frequently referred to in this paper as shadow cells, were interpolated in

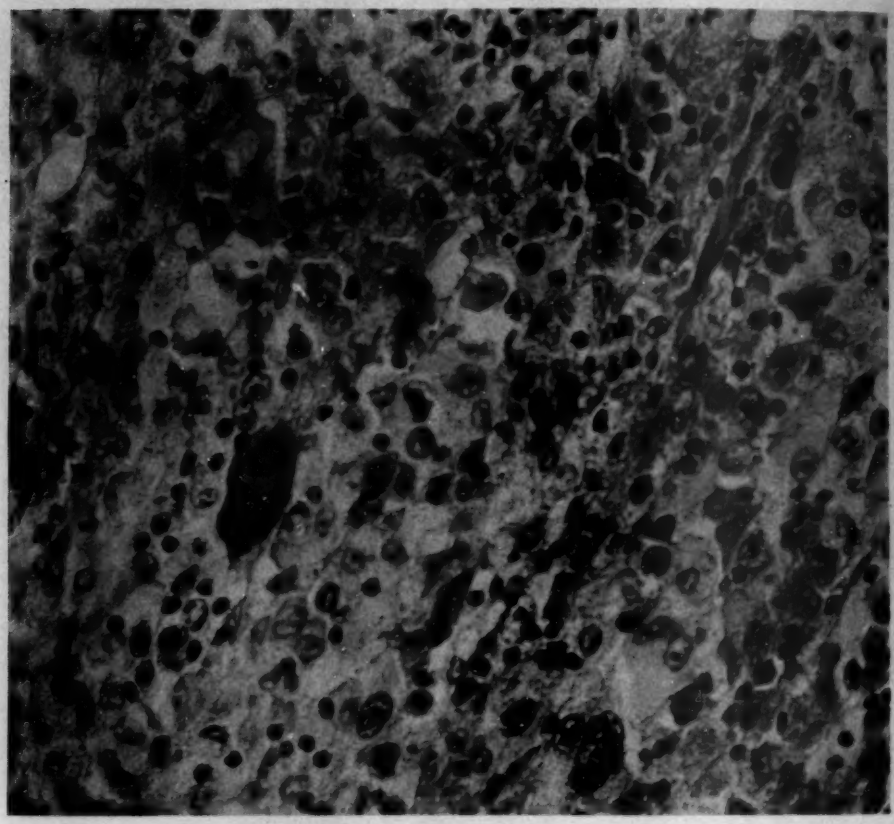

Fig. 10 (part III, case 2).—Section from the same paraffin block as the sections in figures 8 and 9, illustrating a lesion resembling giant cell sarcoma.

considerable numbers. The groundwork of this cellular conglomerate consisted of pinkish staining syncytium.

The patient was seen again Aug. 31, 1937, and new developments were noted in the form of an enlargement in the right axilla, measuring about 5 cm. in diameter, together with an increase in the size of the inguinal nodes. The mass in the right axilla was removed September 17. Microscopic examination revealed widespread overgrowth of mature connective tissue strands, many of which ran parallel with one another. In the interstices were innumerable large, deeply

hyperchromatic cells with nuclei of many different shapes, the cytoplasm of which, when discernible, was smooth and bright pink. Polymorphonuclear eosinophils were scattered through the interstices in countless numbers. Giant cells of the megakaryocytic type were detected in moderate numbers (fig. 11).

Comment.—The microscopic features revealed by the second of the three specimens removed from this patient presented extraordinary deviations from the changes usually met with in Hodgkin's disease. The first node removed showed the changes characteristic of Hodgkin's disease. The second node revealed equally characteristic changes of giant follicular lymphadenopathy in addition to an overgrowth of cells suggesting a spindle and giant cell sarcoma with,

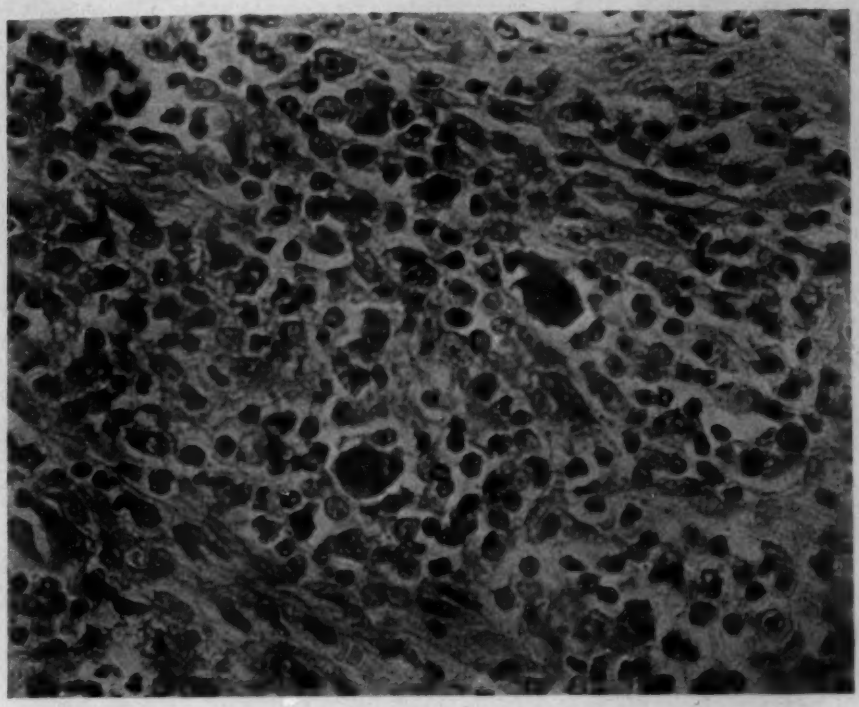

Fig. 11 (part III, case 2).—Section from third biopsy specimen, illustrating the histologic picture of Hodgkin's disease.

however, an occasional giant cell of the megakaryocytic type. The occurrence of giant follicles in the same lymph node in company with the remarkable changes just enumerated constitutes of itself an astonishing and, in my own experience, unique picture. To explain the presence of giant lymph follicles as a feature secondary to the other changes in the same node is contrary to experience in the study of Hodgkin's disease at Bellevue Hospital, and such a view is not included in the customary histologic descriptions of Hodgkin's disease as revealed in the literature. To check this impression, the necropsy records of 42 cases of Hodgkin's disease at Bellevue Hospital were selected indiscriminately, and in not a single instance was it found that lymph follicles of any description were present in

the diseased nodes. I conclude that the lymph node under discussion, namely, the second to be removed, was primarily the seat of giant follicular lymphadenopathy and that the association of Hodgkin's disease was sequential. Whether in the rest of the nodes involved the latter condition was likewise preceded by hyperplastic changes in the follicles is, of course, problematic.

Duration of Illness.—The duration of illness had been approximately two years. Permission for necropsy was not obtained.

CASE 3.—A colonel in the United States Army, aged 39, was admitted to the Letterman General Hospital, San Francisco, Aug. 29 and died Oct. 14, 1928. The clinical history and necropsy protocol, together with tissue and microscopic preparations, were sent to me from the United States Army Medical Museum by Capt. Hugh R. Gilmore Jr., acting curator.

The patient contracted influenza in the pandemic of 1918. Following this, he had an infected maxillary antrum, for which a radical operation was performed in 1921. In the interim, moderate generalized superficial lymphadenopathy developed and later, enlargement of the spleen. At the Fitzsimons General Hospital, Denver, in the latter part of 1924, it was noted that the spleen reached the level of the crest of the left ilium and that the inguinal lymph nodes on the right side approximated the size of a "man's fist." Roentgen radiation applied superficially to the enlarged nodes and roentgen radiation of high voltage to the spleen were followed by rapid diminution in the size of both nodes and spleen. The reduced size of the spleen remained stationary for two years. In 1925 and 1926, at the annual physical examinations, superficial lymph node enlargements were present. In January 1927 it was observed that the spleen had enlarged still further. The roentgen therapy was repeated. In January 1928, at the annual physical examinations, no splenic or lymph node enlargements were detected.

In 1936 Capt. Hugh R. Gilmore Jr. sent me the original microscopic preparations which were made in 1921 and examined by me in 1927, together with seven or eight other preparations which had been made in 1921 but which I had not had the opportunity to examine in 1927. The microscopic sections which I examined in 1927, as already recorded, showed complete replacement of the lymph node by numerical and dimensional hyperplasia of the lymph follicles.

Microscopic examination of the other seven or eight sections of the same lymph nodes removed in 1921 and sent to me by Captain Gilmore in 1936 revealed a different picture. In addition to numerous hyperplastic but otherwise well preserved lymph follicles, there were numbers of massive follicular remains of variable shapes (fig. 12), many of them fused, that were composed almost exclusively of hyperchromatic embryonal cells of the large lymphocytic type, while the body of the lymph node (fig. 13), the capsule and the paranodal fat were infiltrated by hordes of cells of an essentially identical character (fig. 14). On high magnification a sprinkling of large hypochromatic, or shadow cells, was apparent.

Necropsy.—This was done by Capt., now Major, V. H. Cornell, M.C., U. S. A., Oct. 14, 1928. There were no superficial lymph node enlargements. The mesenteric nodes were few and only slightly enlarged. All of the preaortic and retroperitoneal nodes were enlarged, the largest measuring about 3 cm. in diameter. The spleen weighed 830 Gm. and was soft and congested.

Microscopic Examination.—Among the tissues removed at necropsy and sent to me by Captain Gilmore was a lymph node which on microscopic examination showed almost complete replacement by connective tissue together with large

Fig. 12 (part III, case 3).—Fused and ruptured follicles in a lymph node.

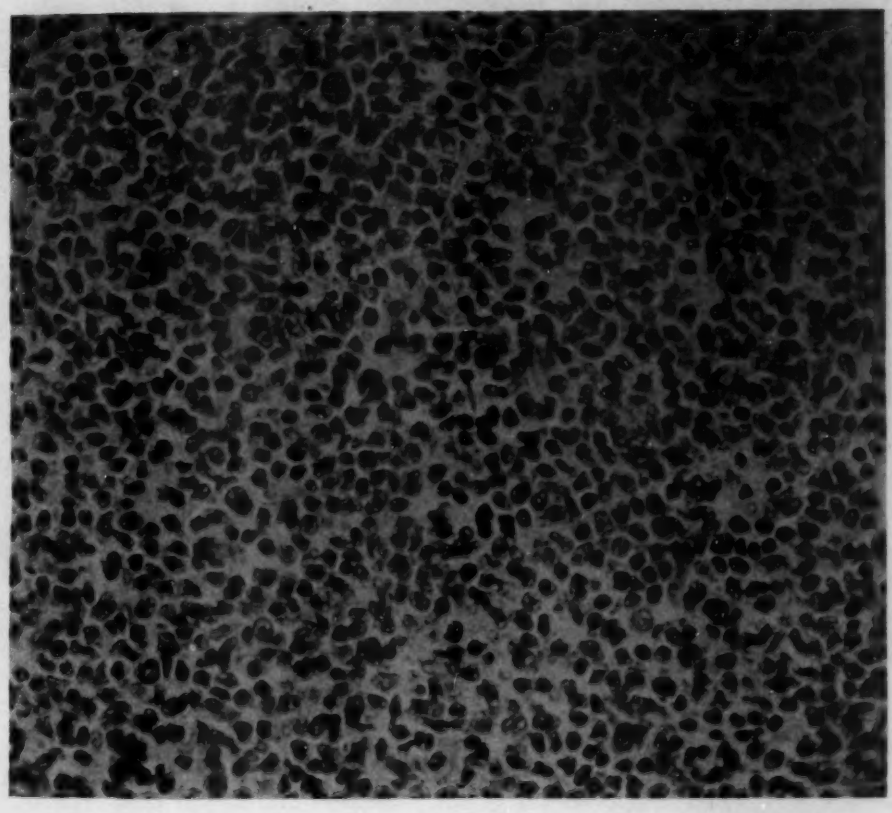

Fig. 13 (part III, case 3).—Polymorphous cell sarcoma occurring in the lymph node depicted in figure 12. See figures 4 and 6.

areas made up of a filmy stroma in which were embedded moderate numbers of small lymphocytes, numerous large mononuclear cells and a few giant cells of the megakaryocytic variety (fig. 15).

A formaldehyde-fixed portion of the spleen, likewise sent to me by Captain Gilmore, showed to the naked eye, embedded in its substance, innumerable whitish specks of irregular contour. The latter revealed themselves on microscopic examination as remnants of massive collapsed follicles, fairly sharply defined, oval or rounded, some of them fused and containing two, sometimes three or four

Fig. 14 (part III, case 3).—Low power photomicrograph illustrating infiltration of the capsule of the lymph node and the paranodal fat in the node depicted in figure 13.

arterioles, eccentrically placed, around which were gathered variable numbers of small lymphocytes and large mononuclear cells together with great numbers of massive cells of the megakaryocytic variety (fig. 16).

Duration of Illness.—The duration of illness was approximately eight years.

Case 4.—A woman aged 31, white, was admitted to the Hospital for the Ruptured and Crippled Dec. 15, 1930, and died Nov. 4, 1935. She was a patient

of Dr. Bradley Coley. About two and one-half years before admission to the hospital (June 1928) enlargement of a lymph node in one groin was noticed, followed soon thereafter by enlargement of lymph nodes in both axillae and in the right cervical region. The spleen at this time was not palpably enlarged. The enlargement of these lymph nodes did not seem to interfere with the activities of life. In fact, the patient was able to take dancing lessons.

At the time of admission to the hospital there was a mass of lymph nodes in the left inguinal region that was described as of about the size of an orange;

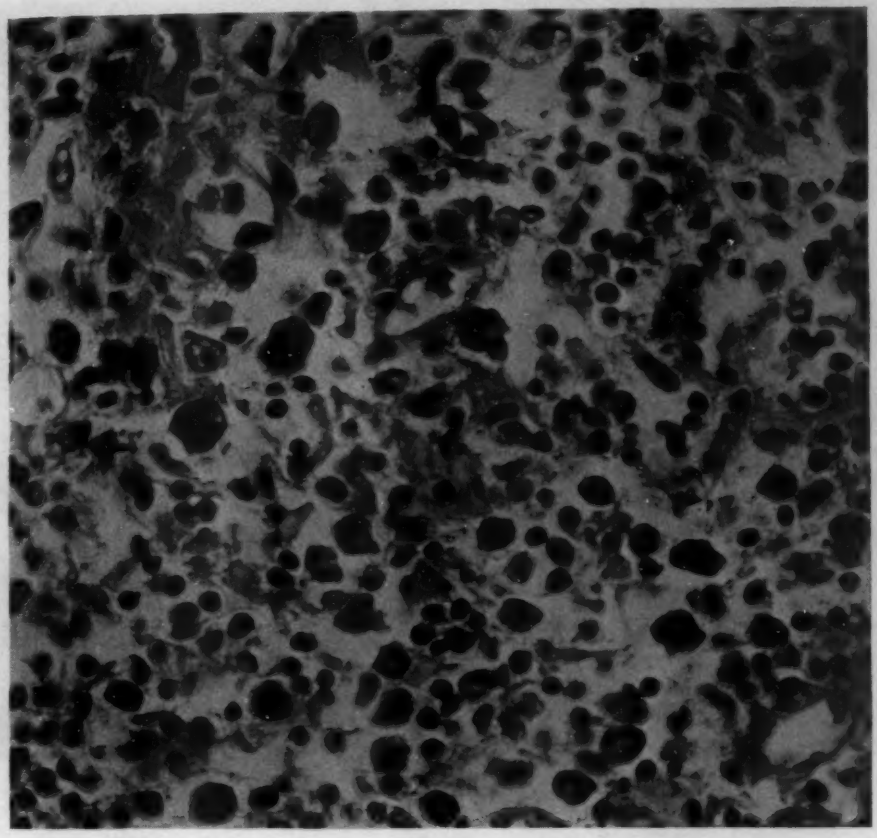

Fig. 15 (part III, case 3).—Hodgkin's disease of a lymph node.

also there were a few enlarged nodes in the right inguinal region and three enlarged nodes in the right axilla, each about 3 cm., in diameter. In the left axilla were two smaller nodes, each about 1 cm. in diameter. In the submental region were two enlarged nodes, one 3 cm. and the other 2 cm. in diameter. The tip of the spleen was palpable beneath the left costal margin.

The blood count was within normal limits.

In April 1929 the patient was in the Presbyterian Hospital, New York, where a solitary enlarged lymph node was removed.

The patient was discharged from the Hospital for the Ruptured and Crippled and readmitted Nov. 11, 1931. She received a prolonged course of roentgen treatment. In February 1932 it was seen that enlargement of the lymph nodes had disappeared. From February 1932 until September 1933 she remained free from detectable enlargement of lymph nodes with the exception of occasional enlargement of a node in the right axilla and some suspected enlargement of nodes in the retroperitoneal region. For the latter she received roentgen exposures both at the Hospital for the Ruptured and Crippled and at the Memorial Hospital

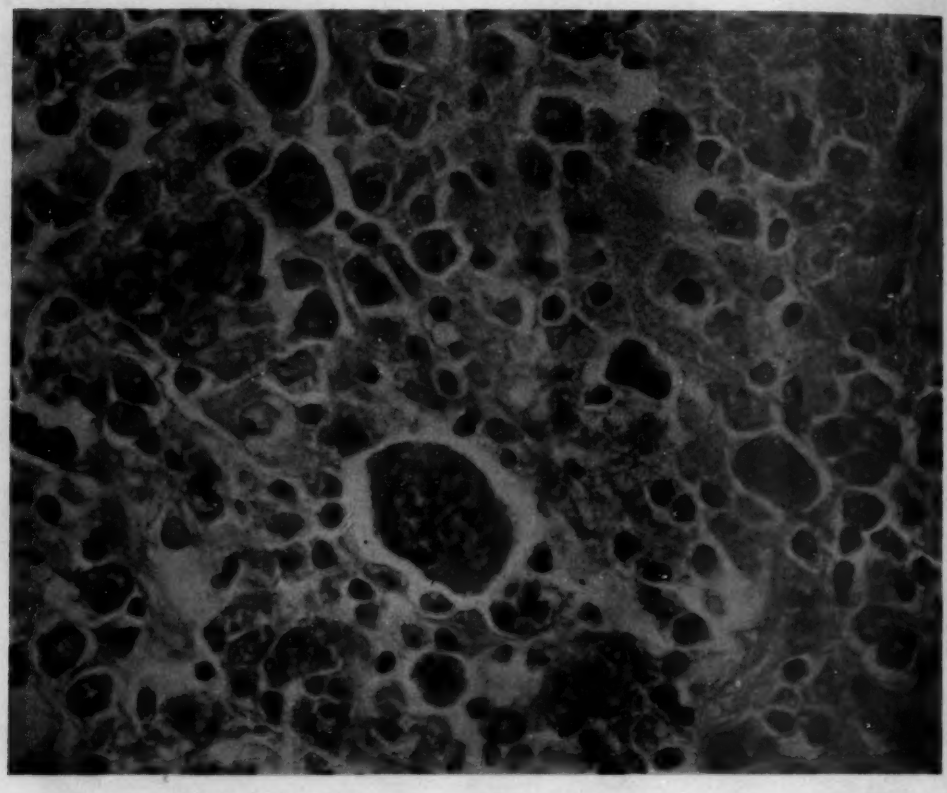

Fig. 16 (part III, case 3).—Hodgkin's disease of the spleen.

for the Treatment of Cancer and Allied Diseases, over a period of one year and seven months. By this time the spleen had enlarged noticeably and was palpable about 3 cm. below the left costal margin. Also in this length of time edema of the lower extremities had developed, and on several occasions large quantities of straw-colored fluid were aspirated from the chest. From this time until her death, two years and three months later, the patient presented moderately enlarged nodes in various parts of the body, and the spleen remained palpable, for all of which roentgen therapy was administered. Despite this and two transfusions of whole blood of 500 cc. each, given eleven days apart, the patient continued to grow weaker. She began to have moderately severe secondary anemia; the edema

of the lower extremities increased, effusions into the thoracic cavities occurred at closer intervals, and the patient died Nov. 4, 1935, after an illness of seven years and five months.

In April 1929 a lymph node was removed at the Presbyterian Hospital. A microscopic section of this node was given to me by Dr. A. P. Stout. Microscopic examination revealed changes which appeared to me to be identical with those already described in this paper as polymorphous cell sarcoma of the lymph follicles. The architecture of the node was replaced by numerical and dimensional hyperplasia of the follicles, which, although not defined by the customary zone of small lymphocytes, were easily identified. They were composed of large hypochromatic cells of the shadow type and hyperchromatic cells of the type of large lymphocytes in about equal proportions, and the rest of the node was replaced by hordes of infiltrating cells of the same sort.

About eighteen months later an enlarged node was removed at the Hospital for the Ruptured and Crippled, and the observations on it were reported by the late Dr. John E. McWhorter, who regarded the changes as those of giant follicular lymphadenopathy. Dr. McWhorter gave me a number of the microscopic preparations on which this diagnosis was based, and in practically every one of them the same histologic picture prevailed, namely, that of numerical and dimensional hyperplasia of the lymphoid follicles, which were closely packed, rounded, well circumscribed by small lymphocytes and composed almost purely of hyperchromatic embryonal follicular cells of the large lymphocytic type. The intervening tissues were not invaded and were made up of small lymphocytes.

Necropsy.—Postmortem examination showed to the naked eye remarkably few changes of interest in the present connection. The spleen weighed 500 Gm. and was fleshy in consistence. The lymph nodes throughout the body were scarcely recognizable as such and were subsequently found to be almost completely replaced by fibrous tissue. Microscopic sections of the spleen, on the other hand, revealed almost complete replacement of its normal architecture by an overgrowth of moderately richly fibroblastic connective tissue, in which the lymphoid follicles were almost completely obliterated, the remnants consisting of collapsed and sclerotic arterioles surrounded by lymphocytes, which were larger than those normally encountered and had among them an occasional mononuclear giant cell. Scattered through the pulp were moderate numbers of giant cells of the megakaryocytic type.

Duration of Illness.—The duration of illness was eight years.

Case 5.—A 47 year old laborer was admitted to St. Vincent's Hospital April 26 and was discharged May 6, 1937. He was referred by Dr. Thomas Martin through Dr. A. Rottino, pathologist. He was admitted because of a swelling in the right groin that he had noticed eight months before. At operation four masses of solid, firm tissue were removed. They weighed together 180 Gm., the largest measuring 11 by 4 by 4 cm. On section the cut surface presented a uniformly grayish brown surface. In the right axilla a firm pea-sized node was felt. A hard, smooth mass was felt through the abdominal wall on the left side in the region of the third and fourth lumbar vertebrae.

Microscopic examination of the masses removed at operation showed innumerable hyperplastic lymph follicles, some rounded, others elongated and still others presenting a lobulated appearance. Some of them were sharply delimited by zones of small lymphocytes. All of the germinal follicles stained lightly and were composed practically exclusively of large hypochromatic embryonal cells of the

shadow type. The remaining substance of the node was made up largely of islands or streaklike infiltrations of large hypochromatic, shadow-like cells essentially identical morphologically with those described in the germinal areas of the lymph follicles. In other places were large isolated patches of mature connective tissue, diffusely outlined, in and around which were small numbers of small lymphocytes and large numbers of large mononuclear giant cells and multinuclear giant cells of the megakaryocytic type.

Duration of Illness.—The duration of illness was about eight months.

Comment.—In this case microscopic examination revealed follicular lymphadenopathy associated with polymorphous cell sarcoma derived from the lymph follicles and with Hodgkin's disease.

CASE 6.— A man aged 58 was admitted to the Englewood Hospital, Englewood, N. J., Dec. 19, 1936, and died Feb. 19, 1937. He was a patient of Dr. R. K. Tether, of Closter, N. J., referred by Dr. F. T. Fadden Jr., pathologist to the Englewood Hospital. He complained of abdominal distention of five weeks' duration following an "attack of cramps." The abdomen was distended, and there was a fluid wave with shifting dulness. Moderately enlarged lymph nodes were present in both sides of the neck as well as in the groins and axillae. Shortly after admission, 1,400 cc. of cloudy fluid was removed from the abdomen. There was dependent edema of the lower extremities. A large mass was palpated in the abdomen. The blood count was normal.

Necropsy.—Postmortem examination revealed general anasarca. There was a chain of enlarged lymph nodes on each side of the neck. The nodes were firm, discrete and measured from 1 to 2 cm. in diameter. Similarly enlarged nodes were found in both axillae. In the anterior mediastinum was a large mass of lymph nodes, the individual nodes being closely packed. In the retroperitoneal region was a lobulated grayish mass, measuring 10 by 15 by 5 cm., which reached from the eighth dorsal to the second lumbar vertebra. A similar mass, measuring 5 by 6 by 2 cm., lay just below the stomach, and still another lower in the abdomen, which measured 4 by 2 by 0.5 cm. Both masses consisted of aggregations of enlarged nodes. The kidneys were partially buried in these masses. In both inguinal regions were markedly enlarged nodes. The spleen weighed 345 Gm. and on section showed a number of homogeneous grayish nodules from 1 to 2.5 cm. in diameter.

Microscopic Examination.—The lymph nodes removed from the neck two months before the death of the patient showed almost complete replacement by hyperplastic lymph follicles made up of an equal admixture of hypochromatic, or shadow, cells and hyperchromatic cells of the large lymphocytic type and hordes of interfollicular cells of the same variety. All that was recognizable of the original node was a thin rim of small lymphocytes at the extreme periphery.

Microscopic examination of lymph nodes from various parts of the body and of the nodular growths in the several organs showed moderately abundant, irregularly distributed, pinkish staining fibrillar connective tissue, embedded in which were great numbers of large rounded cells with moderately richly chromatic nuclei and a fair amount of pinkish cytoplasm. Small lymphocytes were not discernible. Associated with these cells, in practically all of the numerous sections studied, were huge numbers of giant cells of the megakaryocytic variety.

Comment.—In this case was noted the shortest space of time thus far observed to elapse between the occurrence of polymorphous cell sarcoma of the follicles of lymph nodes and the discovery of Hodgkin's disease in association with it

at necropsy—a period roughly estimated as of from two to three months and one week, depending on one's interpretation of the available clinical data.

CASE 7.—A 31 year old plasterer was admitted to Bellevue Hospital April 14, 1933, and was discharged April 29 from the Second Surgical Service of Dr. Guilford Dudley. He complained of a mass in the left side of the neck. He had not been aware of it until it was pointed out to him by a physician whom he had consulted a few days previously because he had lost 16 pounds (7.3 Kg.) in four or five months' time and had suffered from a tired feeling for about two months.

Physical examination revealed a man with obvious signs of loss of weight. On the left side of the neck under the sternocleidomastoid muscle was an oval mass approximately 5 by 3 by 2 cm. The mass was firm, not tender and freely movable. In the immediate vicinity were three palpably enlarged nodes. An enlarged node was palpable in the right axilla, and several such nodes in the axilla of the opposite side. The spleen could not be felt. Five of the enlarged nodes in the neck were removed. The largest measured 6 by 3.5 by 3 cm. and the others from 1 to 2 cm. in diameter. All of them presented on cut section a granular, yellowish white surface. The granules varied in size from 1 to 5 mm. at the base.

Another group of lymph nodes was removed twenty months later, in January 1935. In the interim the patient received prolonged roentgen therapy. Microscopic examination of the several nodes revealed essentially the same changes.

The capsules of the nodes were thickened, and the substance was irregularly traversed by bands of fibrous tissue. The walls of the blood vessels were sclerotic to a marked degree. The cellular remains of the nodes were nevertheless abundant, and there was widespread numerical and dimensional hyperplasia of the lymph follicles. These varied in size from diminutive ones to those which were of gigantic proportions. In some instances the germinal areas of the better preserved follicles were composed practically entirely of large hypochromatic cells of the shadow sort; in others they showed in addition an admixture of hyperchromatic cells of the large lymphocytic type. Most of the follicles, especially the giant forms, were broken, and their outlines could not be completely followed. Other follicles, relatively well preserved, were easily recognized in large numbers and in various situations. The interfollicular tissues of the node were cellular to an extraordinary degree, the most striking feature being an almost incredible array of polymorphonuclear eosinophils together with great numbers of hyperchromatic cells of the large lymphocytic type. In other fields the latter cells were comparatively few, and the large hypochromatic cells predominated. In still other fields were islands composed of variable numbers of hyperchromatic cells of the large lymphocytic type and small lymphocytes, usually with, but sometimes without, eosinophils, and considerable numbers of giant cells of the megakaryocytic type, some of them lying free among the cells, others embedded in a focal connective tissue reticulum. Silver impregnation revealed no reticulum cells.

The patient returned to the clinic every three months from the date of his discharge on April 29, 1933, until his readmission on Jan. 29, 1935. In the interim he was free from any detectable evidence of enlargements of lymph nodes and had received systematic roentgen therapy. Two weeks before readmission, two pea-sized lymph nodes were felt just to the left of the scar of a former biopsy. The nodes were firm, discrete, oval, freely movable and about 2 cm. in length. In addition, there were two enlarged nodes in the left side of the neck, each measuring about 2.5 cm. These were removed, and their microscopic appearances have just been described. The patient complained of a loss of 10 pounds (4.5

Kg.) in weight. In the course of the next one year and ten months, the patient continued to have roentgen therapy and at the end of that time he had gained in weight and was feeling well. No nodes were palpable, nor was the spleen.

At the present moment (June 1938) the patient's condition is not materially changed.

Duration of Illness.—The duration of illness was five years and one month.

COMMENT

In describing Hodgkin's disease as one of the lesions associated with giant follicular lymphadenopathy, details of the several histologic types of giant cells are omitted, reference being made to them as megakaryocytes or as of the megakaryocytic variety or type, thus indicating the belief that they had their origin in the bone marrow and that they were transplanted into the lymph nodes and elsewhere in Hodgkin's disease—a conception which I had the temerity to advance in 1917.[6] In 1924 I sustained this view by microscopic evidence, using the megakaryocyte of the bone marrow as a starting point, adopting as the intermediary phase Bunting's and Minot's independently discovered megakaryocytes in the blood stream of patients with Hodgkin's disease and finally demonstrating megakaryocytes in small blood vessels in the lymph nodes of patients with Hodgkin's disease.[7] In more recent years Medlar [8] offered substantially the same explanation in support of his interpretation of Hodgkin's disease as a metastasizing tumor, for which he proposed the designation "megakaryoblastoma." However this may be, it seems to me to be true that the megakaryocyte is the one distinguishing cell in the composite of cells customarily accepted as the histologic basis for Hodgkin's disease and that in the absence of the megakaryocyte the diagnosis of Hodgkin's disease cannot be made with assurance.

The association of giant follicular lymphadenopathy with Hodgkin's disease is believed to be brought about indirectly, that is to say, by the deposition in the modified lymph nodes of megakaryocytes from the bone marrow and not by alterations in either the fixed or the mobile cells of the lymph nodes or other organs involved. In this respect Hodgkin's disease is in contrast to the polymorphous cell sarcoma, in which the transformation is directly traceable from one cell into another of the same species without benefit of mitosis.

In contemplating the microscopic features in the cases just outlined one is apt to be impressed by the diversified histogenesis out of which Hodgkin's disease emerges at one time or another as an associated lesion.

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6. Symmers, D.: Arch. Int. Med. **19**:990, 1917.
7. Symmers, D.: Am. J. M. Sc. **167**:157 and 313, 1924.
8. Medlar, E. M.: Am. J. Path. **7**:499, 1931.

IV. ASSOCIATION OF GIANT FOLLICULAR LYMPHADENOPATHY WITH LYMPHATIC LEUKEMIA

CASE 1.—A man aged 38 was admitted to the French Hospital, New York, in October 1936, in the service of Dr. H. A. D. O'Connor. He complained of progressive weakness of nine months' duration.

Physical examination showed, on both sides of the neck and posteriorly thirty or more enlarged lymph nodes, firm, discrete and nontender. Among them, especially in the posterior cervical chain, were several which measured about 2 cm. in diameter and were rounded or almond shaped.

In the right axilla were five or six discrete enlarged nodes, each measuring from 1 to 2 cm. in diameter. The left axilla was not palpated because of a recent surgical wound through which a group of six lymph nodes had been removed a few days before. The excised nodes measured from 1 to 1.5 cm. in diameter and were discrete and yellowish white. Dr. O'Connor, who removed them, stated that a number of similarly enlarged nodes had been allowed to remain. In both groins were clusters of enlarged nodes, all of them discrete and firm, many of them shotlike, others varying in size from 1 to 1.5 cm. Nodes along the line of the saphenous vein on both sides were enlarged to the number of four or five, all measuring about 1.5 cm. in diameter. The spleen was massively enlarged, reaching almost to the level of the corresponding ilium, whence it could be traced upward and inward to within 3 or 4 cm. of the median line. The organ was firm and not tender and appeared to be smooth.

Microscopic examination of the excised lymph nodes showed almost complete replacement by hyperplastic follicles, some of them large and others of medium size, while a few were fused. The hyperplastic follicles were for the most part closely packed and separated by small lymphocytes. The cells of the germinal areas consisted practically entirely of hyperchromatic embryonal cells of the large lymphocytic type, with a few large hypochromatic, or shadow, cells and fair numbers of transitional forms.

Blood counts, which were made on innumerable occasions, showed progressive secondary anemia. The white blood cells numbered from 4,400 to 5,600; lymphocytes, from 24 to 40 per cent, with an occasional rise to 65 per cent; red blood cells, from 2,200,000 to 3,750,000; the hemoglobin content was from 20 to 70 per cent.

The patient was first treated by roentgen ray exposures but reacted badly. Blood transfusions were resorted to, but the reaction was so alarming that this method was abandoned. In the meantime the anemia was growing worse, and the patient's life was despaired of. Finally, Dr. O'Connor prescribed a proprietary preparation of iron, injections of which were followed by noteworthy increases in the hemoglobin and in the number of red cells and by improvement in the patient's general health. The lymph nodes and spleen remained as described.

The patient was discharged from the hospital Jan. 20, 1937 and was readmitted May 11.

Removal of the spleen was now contemplated. On May 12, however, it was found that the red blood cell count was 3,020,000, the hemoglobin 70 per cent and the white blood cell count 22,300, of which 92 per cent were lymphocytes and 8 per cent polymorphonuclear neutrophils. On May 20 the red blood cell count was 2,730,000 and the white blood cell count 22,400, with polymorphonuclears 16 per cent and lymphocytes 84 per cent. Operation was abandoned and the patient allowed to go home.

At the time of readmission the lymph nodes in the neck were noticeably more numerous and larger, the individual nodes measuring from 3 to 4 cm. in diameter,

the axillary nodes from 2 to 3 cm. in diameter and the inguinal and subinguinal nodes from 2 to 4 cm. in diameter. All of them were discrete, moderately firm and freely movable. The spleen was still more massively enlarged; it was easily lost in the pelvis on the left side but could be traced inward for a distance of about 5 cm. beyond the median line. The liver was palpable about a hand-breadth below the costal slope on the right side.

The patient died in August 1937. Permission for a necropsy was not obtainable.

CASE 2.—A policeman aged 34 was admitted to Bellevue Hospital Sept. 9 and died Nov. 3, 1931. He entered the hospital with massive swelling of the left leg and symptoms of fluid in the pleural cavities together with enormous generalized enlargement of the superficial lymph nodes and enlargement of the spleen extending as far downward as the level of the umbilicus. Innumerable blood counts revealed leukocytosis, the numbers of white cells varying from 18,600 to 40,500, with lymphocytes constituting from 90 to 98 per cent.

Necropsy.—The lymph nodes throughout the body were enlarged; some were discrete, and some were in chainlike formation, but most of them were fused to form huge masses occupying the anterior mediastinum and the tracheobronchial, mesenteric and retroperitoneal regions. The spleen was enlarged and weighed 1,050 Gm., measuring 25 by 12 by 8 cm. The cut surface was stippled with small whitish areas. Both pleural cavities and the peritoneum contained large quantities of serous fluid.

Microscopic Examination.—The various viscera revealed widespread lymphocytic infiltration and, in places, circumscribed lymphoid deposits (fig. 17). In some of the lymph nodes were the remains of enormous lymph follicles, partly or completely surrounded by zones of small lymphocytes (fig. 18); the parenchyma was packed by somewhat larger lymphocytes, and the germinal areas, which stained fairly darkly, were made up almost exclusively of the same large cells.

CASE 3.—A woman of 32 years was admitted to the clinic of the Memorial Hospital for the Treatment of Cancer and Allied Diseases May 1, 1931.[8] She stated that her illness had begun one year before with enlarged cervical lymph nodes. For about three months before that time the abdomen had been enlarging. Examination showed slight general lymphadenopathy and massive enlargement of the spleen, the latter extending to the right of the midline and downward into the pelvis. Biopsy of an axillary lymph node was done and the microscopic preparations were interpreted by Dr. Fred Stewart as giant follicular lymphoma or, as it is characterized in this paper, giant follicular lymphadenopathy. The red blood cell count on admission was [9] 4,050,000; the white cell count was 12,000, with poly-

9. In Dr. Craver's publication the blood count on admission is recorded as "7,800 white cells, with 38 per cent small lymphocytes, 7 per cent large lymphocytes, 7 per cent eosinophiles, and only 39 per cent polynuclear cells"—a total of 91 per cent of leukocytes. When I called Dr. Craver's attention to this he replied that the missing 9 per cent consisted of transitional cells and that he had purposely omitted them in order to emphasize the relative proportion of lymphocytes and polymorphonuclear cells. On inquiry into the record, however, he found that the wrong count had been given in his paper, and he substituted the figures used in this paper as the correct count on admission. I mention this detail in order that any one who might read this paper and compare it with Dr. Craver's publication may not be misled by the difference between the white cell counts in the case as originally recorded by Dr. Craver and as corrected by him but apparently misquoted by me.

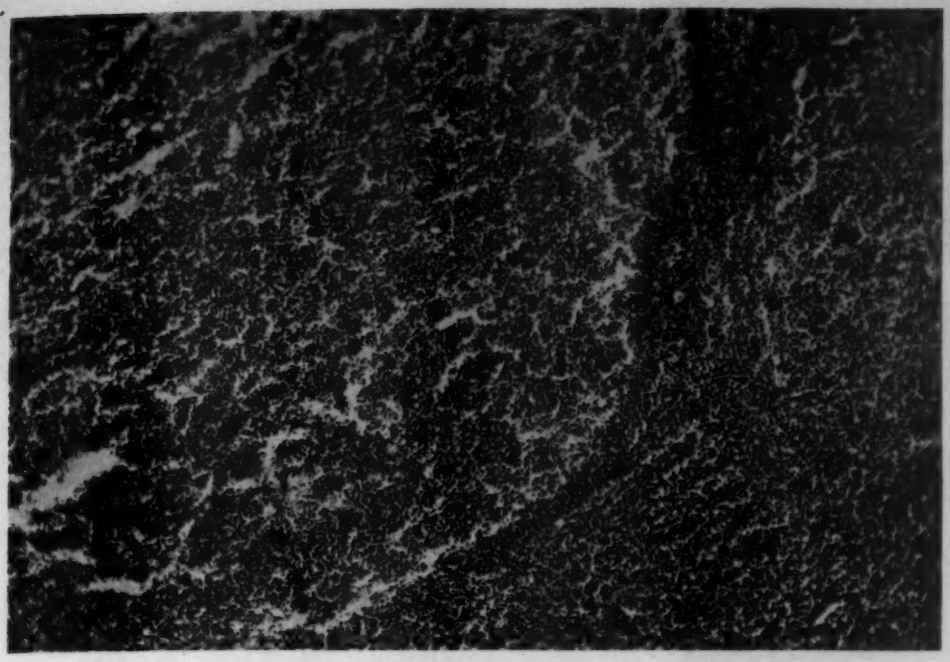

Fig. 17 (part IV, case 2).—Massive hyperplasia of the lymph follicles in lymphatic leukemia.

Fig. 18 (part IV, case 2).—Lymphocytic infiltration of the liver in lymphatic leukemia.

nuclear neutrophils 23 per cent, large lymphocytes 3 per cent, small lymphocytes 71 per cent, transitionals 2 per cent and basophils 1 per cent. Blood counts were done at intervals for a period of about three years. A complete set of counts was given to me by Dr. Craver. During these years the white cell counts, with the exception of one on admission and one on the day of death, revealed leukopenia, varying from 5,400 to 1,800, the average of forty-six counts being 4,409, with the lymphocytes varying from 24 to 74 per cent except on the day of death, when the total count consisted of 151,000 white cells, all of them lymphocytes.

On August 7, 1934, the patient died. Necropsy was performed. Dr. Craver's comment is: "This case, which had run a leukopenic course for three years, and in which a biopsy had shown giant follicular lymphoma, was found at autopsy to be lymphatic leukemia, with infiltration of liver, spleen, stomach, kidneys, adrenals, and all superficial and deep nodes . . ."

CASE 4.—The patient, a man aged 50, was seen for the first time by Dr. R. D. Baker,[10a] of Summit, N. J., Oct. 22, 1926, and died in September 1930. He complained that the nodes behind the ears and on the back of the neck had been swollen for several months. He stated also that he suffered from occasional "hot and cold" feelings, irregular discomfort in the upper part of the abdomen, sleeplessness, headache, nervousness, nausea and a feeling of being "very tired."

Physical examination revealed that the tip of the spleen was palpable and tender and that there were enlarged lymph nodes behind the ears just above the insertions of the sternocleidomastoid muscles, together with many smaller cervical nodes, a few enlarged and tender occipital nodes and a few enlarged inguinal nodes on both sides. The two blood counts were described as normal. One of the nodes behind the ear was removed and examined by Dr. H. S. Martland, of Newark, N. J., who made the diagnosis of giant lymph follicle hyperplasia or, as it is called in this paper, giant follicular lymphadenopathy. Dr. Martland's diagnosis was confirmed by Dr. George Baehr. Roentgen treatment was given over the enlarged lymph nodes and spleen. The spleen became impalpable, and the lymph nodes diminished greatly in size. From time to time, however, the spleen increased in size and was palpable from 1 to 3 fingerbreadths below the ribs on full inspiration. The most troublesome and painful nodes were in the inguinal region on the left side and in the external retrocrural region. The superficial lymph nodes likewise showed variation in size from time to time but never any marked increase in size. About June 1929 it was noted that the abdominal nodes were markedly increased in size and painful and that there was evidence of enlargement in some of the mediastinal nodes.[10b] At this time the white blood cells numbered 15,000, 91 per cent of which were lymphocytes and 9 per cent polymorphonuclear neutrophils. Dr. Baehr again saw the patient and concurred in Dr. Baker's diagnosis of chronic lymphatic leukemia.

Comment.—In 1926 both Baehr and Martland agreed that the changes in a lymph node removed from the neck of Davis' patient were those of giant lymph follicle hyperplasia. In 1929 the same patient presented clinical and hematologic signs of lymphatic leukemia and was seen by Baehr, who confirmed that diagnosis. In 1932 Baehr,[11] in a paper read before the American Association of Physicians, gave it as his opinion that all cases of giant lymph follicle hyperplasia (follicular

10. Baker, R. D.: (*a*) J. A. M. A. **88**:2035, 1927; (*b*) personal communication to the author.

11. Baehr, G.: Tr. A. Am. Physicians **47**:330, 1932.

lymphadenopathy with splenomegaly) are primarily instances of lymphosarcoma and called the condition follicular lymphoblastoma. Baehr's paper is largely a clinical presentation and has little to say from the standpoint of pathology in confirmation of the primary lymphosarcomatous nature of the process. Although I find myself in conflict with distinguished opinion on the interpretation of the original hyperplastic process, I am nevertheless pleased that the same opinion has confirmed the fact emphasized in this paper that follicular lymphoblastoma, follicular lymphadenopathy or whatever its academic status may be is capable of becoming associated with lymphatic leukemia.

CONCLUSIONS

Giant follicular lymphadenopathy with or without splenomegaly is a clinical and pathologic entity. Clinically, it resembles Hodgkin's disease, certain forms of lymphosarcoma, lymphatic leukemia and the like. Histologically, the changes are characteristic and consist in numerical and dimensional hyperplasia of the lymph follicles of lymph nodes and spleen. The condition is probably of "toxic" or "inflammatory" origin and is usually amenable to mild roentgen therapy.

Giant follicular lymphadenopathy is capable of direct transformation into a heretofore undescribed polymorphous cell sarcoma having multiple foci of origin in hyperplastic lymph follicles.

Giant follicular lymphadenopathy with splenomegaly is capable of assuming the histologic features of Hodgkin's disease as added associated phenomena and not as a process of transformation. It may likewise become associated with the changes of lymphatic leukemia.

The term "reticulum cell lymphosarcoma" should be abandoned as misleading. No such tumor has been shown to exist. The tumor so designated is in reality the large round cell sarcoma of lymph nodes and is to be distinguished from the polymorphous cell sarcoma of lymph follicles described in this paper.

The disease described in this paper under the histologic designation "necrotic folliculitis of lymph nodes and spleen" is believed to be unique in that, among other things, it represents a heretofore unrecorded phase in the evolution of giant follicular lymphadenopathy with splenomegaly.

HISTOLOGY OF THE BONE MARROW IN APLASTIC ANEMIA

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The exact details of the alterations of the bone marrow in aplastic anemia have received little attention, notwithstanding the considerable number of comprehensive reviews of the clinical aspects of the subject. The condition has been so uncommon and interest in the minute histologic changes of the marrow has been so slight until recent years that exceedingly few detailed studies are available. In the course of a clinical, experimental and pathologic study of 69 cases of refractory anemia, it was possible to study the living cells of the sternal marrow by the supravital technic of Sabin [1] in 41 cases of aplastic anemia. These observations with the supravital technic were correlated with observations on smears and sections of the same tissue prepared by fixation and staining technics and of further material obtained in certain instances post mortem. On the basis of the facts derived from these studies, it has been possible to arrive at a clearer understanding of the pleomorphic clinical pictures encountered in aplastic anemia and of the histologic basis for the failure of hemopoiesis.

LITERATURE

Interest in the changes of the bone marrow in aplastic anemia has recently been stimulated by the communication of Thompson, Richter and Edsall,[2] in which the subject was thoroughly reviewed. These authors reported 13 cases of the disease in which histologic studies of the bone marrow were available. In 3 of these cases hypoplasia of the marrow elements was present; in 2 the marrow appeared normal, and in 8 a degree of cellularity greater than normal was observed. In all of the cases reported there was a progressive fatal anemia which failed to respond to the ordinary hemopoietic agents, given in the

From the Hospital of the Rockefeller Institute for Medical Research.

1. Sabin, F. R.: Bull. Johns Hopkins Hosp. **34**:277, 1923.

2. Thompson, W. P.; Richter, N. M., and Edsall, K. S.: Am. J. M. Sc. **187**: 77, 1934.

usual dosage. From the fact that hyperplasia was frequently observed, it is clear that the lack of production of the adult cellular elements of the blood is not necessarily due to a lack of immature forms in the bone marrow. These studies confirmed and extended the observations of Sheard,[3] who pointed out that hyperplasia of marrow elements, rather than aplasia, might be present in cases of anemia in which little evidence of regeneration was shown by the peripheral blood. Blumer[4] and others have also reported observing cellular marrow at autopsy in cases of anemia in which during life the condition had been supposed to be associated with hypoplasia of the marrow. Hypercellularity of the marrow has been a particularly common observation in those instances in which certain chemical substances could be identified as causative of the anemia. Such hypercellularity has been reported by Turnbull[5] in trinitrotoluene poisoning, by Martland[6] in radium poisoning and by Andersen,[7] Martland[8] and Cabot[9] in benzene poisoning. Although a number of other reports of the changes of the marrow in aplastic anemia exist, they are so lacking in detail that they add little applicable information.

METHODS

Specimens of sternal marrow were removed for biopsy according to the technic described by Rhoads and Castle.[10] Smear preparations were made immediately on slides stained with neutral red and janus green by the technic of Sabin.[1] The smears were examined immediately in a warm box kept at a temperature of 37 C. By expressing the cellular tissue from among the bone spicules, excellent preparations could be obtained. Differential counts were made of from 500 to 1,000 cells from at least 10 different oil immersion fields.

For the study of stained sections, the material removed from the sternum was fixed in Zenker's fluid, containing 5 per cent acetic acid, and Zenker's fluid containing, instead of acetic acid, solution of formaldehyde U. S. P. (1:10). The tissue was dehydrated and cleared by the usual technic and was then embedded in paraffin. No attempt was made to decalcify the tissue, since it was found that any available method of decalcification seriously interfered with staining. The sections were cut as thin as possible and were stained with both eosin and methylene blue and by Giemsa's method.

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3. Sheard, A.: A Contribution to the Study of Pernicious Anemia and Aplastic Anemia, New York, William Wood & Company, 1924.

4. Blumer, G.: Bull. Johns Hopkins Hosp. **16**:127, 1905.

5. Turnbull, H. M.: Proc. Roy. Soc. Med. **10**:47, 1916-1917.

6. Martland, H. S.: Am. J. Cancer **15**:2435, 1931.

7. Andersen, D. H.: Am. J. Path. **10**:101, 1934.

8. Martland, H. S., cited by Hamilton, A.: Arch. Path. **11**:626, 1931.

9. Bleeding from the Gums, Cabot Case 13321, Boston M. & S. J. **197**:236, 1927.

10. Rhoads, C. P., and Castle, W. B.: Am. J. Path. **9**:813, 1933.

RESULTS

On the basis of the histologic changes observed in the stained preparations, it is possible to divide the cases into five general groups. Each group will be discussed as a whole, and the cellular changes characteristic of the group will be described as observed both in the supravitally stained and in the fixed preparations.

Biopsies of sternal marrow were done in 63 of the 69 cases. The scarcity of marrow cells or the difficulty in obtaining a suitable preparation limited the number of supravital studies to 41. Both biopsy and autopsy specimens of marrow were available in 26 cases whereas only autopsy material was obtained in 6 cases.

At the outset there is required a brief discussion of the terms which will be employed in describing the cells of the marrow. The review published by Vaughan and Turnbull [11] is a useful reference as far as the cells seen in fixed and stained sections are concerned, and wherever possible the terms suggested by these authors have been used. Thus the presumed pluripotential stem cells of the marrow are termed hemocytoblasts and are assumed to be the precursors of granular leukocytes, erythrocytes and lymphocytes. The hemocytoblast may be described as a large cell with a pale nongranular basophilic cytoplasm, a large nucleus containing multiple delicate threads of chromatin and frequently one or more nucleoli. It is inferred from these morphologic aspects that the hemocytoblast is the cell which is present in large numbers in the bone marrow of patients with pernicious anemia, a cell termed a megaloblast by Peabody [12] in his classic study of the subject. It appears, however, that the term "megaloblast" should be reserved for those early erythrocytes of characteristic appearance which are seen in sections of a human embryo 0.5 cm. long. Hemocytoblasts are stated to develop through erythroblasts into normoblasts by a reduction in size, an increase in the intensity of nuclear basophilism, a progressive diminution in the basophilia of the cytoplasm and finally an acquisition of hemoglobin by the cytoplasm.

In the material on which this communication is based, all of the steps in cell maturation described by Vaughan and Turnbull are easily recognized. Cells of a type which is difficult to fit into their classification are also present and prominent. This type of cell is small and round, contains a narrow rim of basophilic cytoplasm and has a round nucleus filled with a mass of densely matted, deeply staining chromatin. When cells of this type are studied in the living state, supravitally stained by neutral red and janus green, they are seen to

11. Vaughan, J. M.: The Anaemias, with Notes on Normal and Pathological Erythropoiesis by H. M. Turnbull, London, Oxford University Press, 1934.

12. Peabody, F. W.: Am. J. Path. 3:179, 1927.

be distinctly different from the lymphocytes of the circulating blood, to which they bear a morphologic resemblance. They have less cytoplasm than do lymphocytes and no cytoplasmic granules staining red or green; they are nonmotile, and they have a somewhat denser arrangement of the nuclear chromatin than do lymphocytes. Sabin [13] termed these cells primitive and considered them to be very young forms, possibly antecedent even to hemocytoblasts. No attempt will be made here to ascribe to these primitive cells their proper place in the scheme of hemopoietic maturation, but since in aplastic anemia they are encountered in the marrow in large numbers they deserve special mention.

The terminology of Cunningham, Sabin and Doan [14] has been followed in describing the cells of the marrow as they appear when stained supravitally. When studied by that method, granulocytes and their precursors need no description. Under the heading of myeloblasts are included cells with a fairly large amount of cytoplasm containing no specific granules. The nucleus is of good size and contains a few threads of rather pale, translucent chromatin and one or more nucleoli. It is inferred that this cell is the hemocytoblast of Vaughan and Turnbull [11] or the megaloblast of Peabody,[12] but conclusive evidence of the fact is not at hand.

Among the cells of the erythropoietic series, the normoblasts need no discussion. Under the term "erythroblast" are included cells with a variable amount of cytoplasm, which is rather deeply basophilic and may contain hemoglobin. The nucleus is round or slightly ovoid and contains a heavy network of chromatin.

It is clearly recognized that the supravital preparation is a highly artificial one, involving, as it does, an inevitable tendency to spread loosely attached cells on the slide and to allow more firmly attached groups to remain behind. This fact may explain the apparent discrepancy between the numbers of myeloblasts and of early erythroblasts seen in supravital spreads and the numbers appearing in sections of fixed tissue. It is considered, however, that this discrepancy does not detract seriously from the validity of the general conclusions which have been drawn from the study.

Group 1. Aplastic Anemia with Aplastic Marrow.—In this group, 28 marrows are available, 13 of which were studied supravitally. The peripheral blood of patients with this condition is characterized by

13. Sabin, F. R.; Miller, F. R.; Smithburn, K. C.; Thomas, R. M., and Hummel, L. E.: J. Exper. Med. **64**:97, 1936.

14. Cunningham, R. S.; Sabin, F. R., and Doan, C. A.: The Development of Leucocytes, Lymphocytes and Monocytes from a Specific Stem-Cell in Adult tissues, Publication 361, Carnegie Institution of Washington, 1925; Contrib. Embryol. **16**:227, 1925.

severe anemia, granulopenia and a decreased number of platelets. The term "aplastic" is applied to what is more accurately termed hypoplastic tissue, for complete aplasia is rarely encountered. Since the term has the sanction of usage, it is employed for the sake of simplicity. Hypoplastic marrows of less cellularity than normal have been supposed to be constantly present in aplastic anemia. Such a sternal marrow is shown in figure 1 *C* and *D* and may be compared with the normal marrow depicted in figure 1 *A* and *B*. There is marked decrease in cellularity with almost complete absence of hemopoietic islands. Isolated groups of from 2 to 4 cells of varying degrees of maturity are seen, but the orderly arrangement of proliferating and maturing cells in islands connected by vascular channels is completely lacking. All the types of cells seen in normal marrows are present, though in reduced numbers. In table 1 are presented in detail the results of supravital studies of 13 marrows of this group; averages of the differential counts are presented in a more concise form in table 6 for comparison with the normal and the averages of the other groups. The major variations from the normal, as shown by these studies, are a drop in the percentage of polymorphonuclear leukocytes, including eosinophils, from 65 in the normal to 30 in the aplastic marrow, together with an increase in the percentage of the primitive cells from 6 in the normal to 27 in this group. At the same time increases occurred in the percentages of myelocytes and normoblasts. This pronounced relative increase of primitive, undifferentiated forms is interpreted as indicating a failure of maturation, which is responsible for the decreased numbers of the circulating blood cells, both granulocytes and erythrocytes. On the other hand, no increase in hemocytoblasts or erythroblasts such as occurs in pernicious anemia is observed in the marrow. Hence, the basic change in the marrows of the aplastic or hypoplastic group may be summed up as a deficiency in number of all hemopoietic cells plus a suppression of maturation of all hemopoietic cells. This change results in a relatively sharp increase in the number of primitive cells at the expense of that of the more adult forms.

Group 2. Aplastic Anemia with Hyperplastic Marrow (Pluricytopenia).—Twenty marrows of this type were examined, 15 of which were studied supravitally. The peripheral blood in the cases included under this heading is characterized by a marked decrease in the numbers of all of the formed elements of the blood, as evidenced by leukopenia, granulopenia, a decreased number of platelets and persistently low erythrocyte levels. Hence, the term "pluricytopenia" may be applied. There is in patients with this condition a striking tendency to necrosis of the mucous membranes, particularly those of the lips, tongue, pharynx and rectum. Bleeding is rarely present other than as a terminal

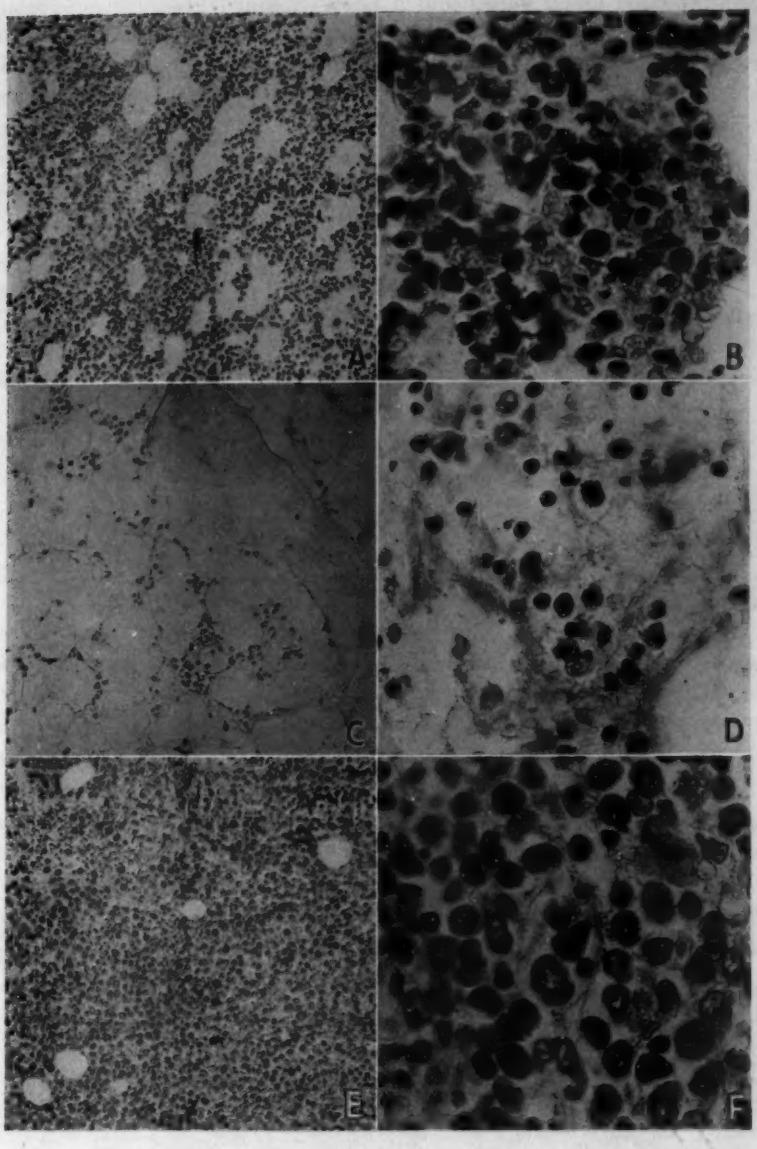

Fig. 1.—*A*, normal sternal marrow; × 125. *B*, normal sternal marrow; × 500. *C*, aplastic sternal marrow; × 125. *D*, aplastic sternal marrow × 500. *E*, hyperplastic sternal marrow; × 125. *F*, hyperplastic sternal marrow; × 500.

feature. Abnormal leukocytes, particularly of the granulocyte series, frequently appear in the blood. In certain instances these cells show well developed lobed nuclei and a poorly defined granular cytoplasmic

TABLE 1.—*Percentages of Different Types of Cells Observed in Sternal Marrow in Thirteen Cases in Which Aplastic Anemia was Associated with Aplastic Marrow (Group 1).*

Case	Neutrophils	Myelocytes A	Myelocytes B	Myelocytes C	Myeloblasts	Eosinophils	Basophils	Normoblasts	Erythroblasts, Late	Erythroblasts, Early	Clasmatocytes	Megakaryocytes	Lymphocytes	Monocytes	Primitive	Unclassified
1.....	30.00	2.00	9.00	20.00	....	4.00	....	8.00	2.00	....	....	...	...	....	24.00	...
2.....	21.40	0.80	2.00	21.00	0.20	0.20	....	20.20	4.40	....	....	...	0.8	....	27.80	0.2
3.....	40.00	1.20	2.00	7.60	0.20	5.80	....	2.80	1.00	0.40	0.20	...	...	....	38.80	...
4.....	9.00	2.20	2.80	9.20	2.00	1.40	....	33.00	2.60	....	....	...	...	....	35.80	...
5.....	6.33	2.66	10.66	19.33	....	2.66	0.33	28.66	3.33	....	....	...	...	1.33	23.66	...
6.....	36.50	3.50	4.50	28.50	1.00	4.00	....	8.00	3.50	....	....	0.5	...	....	10.00	...
7 (a).....	18.60	2.00	5.60	53.60	1.60	0.60	....	3.60	0.80	....	....	...	...	....	13.60	...
(b).....	18.80	1.00	8.00	45.00	....	2.40	....	12.60	0.20	....	....	...	...	....	12.00	...
8.....	34.40	....	2.20	16.20	....	1.00	....	29.80	0.80	....	....	...	0.2	....	15.40	...
9.....	16.33	0.33	1.33	4.00	....	1.00	....	17.00	....	....	....	...	...	....	60.00	...
10.....	44.80	....	1.20	14.20	....	0.40	....	6.20	0.60	....	....	...	...	....	32.60	...
11.....	7.16	0.50	3.50	21.60	....	4.16	....	33.33	3.83	....	0.33	...	...	....	26.60	...
12.....	32.80	0.20	0.80	39.40	....	4.40	....	14.80	2.40	0.40	....	...	0.2	....	4.60	...
13.....	11.00	2.33	4.32	5.66	0.33	0.33	....	29.00	5.66	1.66	....	...	...	....	49.66	...
Average...	27.90	1.30	4.10	21.80	....	2.30	....	17.10	2.20	....	....	...	...	....	26.70	...

TABLE 2.—*Percentages of Different Types of Cells Observed in Sternal Marrow in Fifteen Cases in which Aplastic Anemia was Associated with Hyperplastic Marrow (Group 2).*

Case	Neutrophils	Neutrophils, Round	Myelocytes A	Myelocytes B	Myelocytes C	Myeloblasts	Eosinophils	Basophils	Normoblasts	Erythroblasts, Late	Erythroblasts, Early	Megaloblasts	Clasmatocytes	Megakaryocytes	Lymphocytes	Monocytes	Primitive	Unclassified	Blasts
1	0.40	...	0.80	1.80	2.40	....	0.20	...	2.40	....	....	....	....	....	...	....	85.00	...	7.0
2	1.75	...	9.50	12.10	1.50	....	....	...	4.75	2.12	0.12	....	0.25	1.37	...	6.12	60.22	...	...
3	2.20	...	5.00	5.40	1.40	0.20	2.60	...	4.40	0.40	....	....	0.20	....	...	....	78.20	...	...
4	17.60	...	6.00	9.80	43.20	4.00	1.60	...	12.80	1.00	0.20	....	....	....	...	....	3.80	...	...
5	4.40	...	1.40	0.80	1.20	0.40	1.00	1.2	29.00	54.40	1.60	....	....	....	...	....	4.20	0.4	...
6	29.40	...	2.20	1.80	53.40	1.80	2.60	0.6	2.20	....	....	....	....	....	...	....	6.00	...	...
7	6.20	...	0.20	1.60	5.60	2.40	2.40	...	12.80	....	....	....	....	0.20	...	....	71.00	...	...
8	43.33	...	2.33	9.33	24.66	0.33	6.33	...	3.33	....	....	....	....	....	...	....	10.33	...	...
9	29.40	...	0.80	1.00	13.20	2.20	6.40	...	31.40	6.80	2.60	....	0.20	....	...	....	6.00	...	...
10	1.33	3.33	8.33	6.66	8.30	16.00	0.66	...	19.33	3.66	1.66	....	0.33	....	...	....	30.33	...	...
11	1.00	...	1.55	1.80	0.80	59.60	....	...	2.30	7.90	2.10	0.15	2.40	....	...	....	19.90	0.1	...
12	2.50	...	....	1.00	11.00	1.00	5.00	1.5	9.00	4.50	1.50	....	....	....	8.5	1.50	53.00	...	...
13	0.80	...	....	....	....	....	....	...	1.00	3.80	1.80	....	....	....	0.6	1.60	90.40	...	...
14	18.20	...	2.40	1.60	30.20	4.60	0.80	...	18.00	15.20	3.20	....	....	....	...	....	5.80	...	...
15	9.20	...	3.80	5.60	16.50	2.20	3.00	...	25.60	3.00	0.60	....	0.20	....	...	....	30.20	...	...
Av	11.10	...	2.90	4.00	14.20	6.30	2.10	...	11.80	3.40	1.00	....	....	....	...	....	36.90	...	...

structure. Other cells may resemble myelocytes with a rather sparse, well defined nuclear chromatin network and a very few cytoplasmic granules.

When marrows of this group are studied by supravital staining, tables 2 and 6, they show a sharp decrease in the percentage of polymorphonuclear leukocytes to 13 as contrasted with 65 in normal marrows. There is, on the other hand, an increase in the percentage of myelocytes to 21. The most striking change, however, is the greatly increased number of primitive cells present, which make up 36 per cent of the total. These cells have been described previously in this communication and may be seen clearly in the photomicrograph of the fixed and stained preparation (fig. 1 *E* and *F*). The normal structure of the marrow is obscured by a dense infiltrate of undifferentiated cells, a cellular picture as uniform as that encountered in marrows which have been infiltrated with leukemic tissue.

The objection may well be advanced that cases of this type are, in fact, examples of aleukemic leukemia. Decision as to the correctness of such a view must remain a matter of terminology for the present. If a leukemic blood picture occurring at some time in the course of the disease, leukemic infiltration of organs at autopsy or a leukemic tumor is required for the diagnosis of leukemia, the cases of hyperplastic marrow with pleuricytopenia reported here cannnot be included under that heading. In such cases the predominant cells of the marrow are clearly not lymphocytes, as may be seen by comparing the photomicrographs of a marrow of the group under discussion (fig. 1 *E* and *F*) with the photomicrographs of a marrow infiltrated with the tissue of lymphatic leukemia (fig. 2 *A* and *B*). The histologic picture of the hyperplastic marrow of aplastic anemia is not that ordinarily seen in myeloid leukemia, since there is no tendency toward maturation of the undifferentiated cells to myelocytes and since the predominating cells differ markedly from myeloblasts in structure. Comparison with the photomicrographs of a marrow from a person who had typical myeloid leukemia (fig. 2 *C* and *D*) shows a striking contrast with the change seen in aplastic anemia. Pending further studies, it is felt that the clinical and pathologic evidence justifies placing cases of refractory anemia with undifferentiated or primitive hyperplastic marrow in a separate group.

Group 3. Aplastic Anemia with Active Marrow.—Eleven examples of this group are available, 10 of which were studied supravitally. The clinical course is marked by absence of any symptoms other than those due to the anemia. The progression of the anemia is extremely slow, and if frequent transfusions are given the course may be prolonged for years. Mild leukopenia and granulopenia are features. When studied supravitally (tables 3 and 6), the marrows show more similarity to marrows of pernicious anemia (tables 5 and 6) similarly studied than do the marrows of any other group. There is an increase

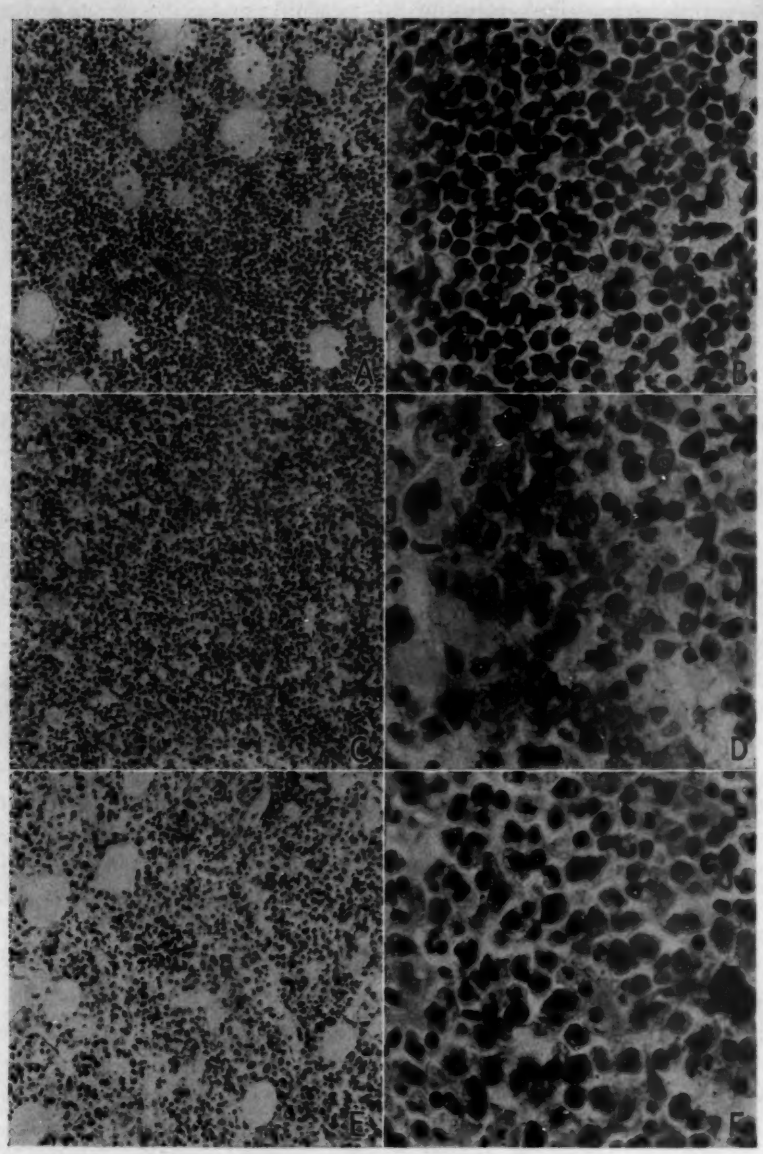

Fig. 2.—*A*, sternal marrow in lymphatic leukemia; × 125. *B*, sternal marrow in lymphatic leukemia; × 500. *C*, sternal marrow in myeloid leukemia; × 125. *D*, sternal marrow in myeloid leukemia; × 500. *E*, active sternal marrow; × 125. *F*, active sternal marrow; × 500.

in the numbers of myelocytes and normoblasts in this group as compared with pernicious anemia, but the total percentage of erythroid cells is almost the same in both conditions. In table 6 the megaloblasts are included with the erythroblasts; less than 1 per cent were found in this aplastic group, whereas 2 per cent were found in the marrows of persons with pernicious anemia.

It is inferred that marrows of this group are those described by Thompson and his co-workers [2] as morphologically normal. There is, however, a definite suppression of maturation of granulocytes to be detected by differential counting. The average percentage of polymorphonuclear leukocytes drops to 24 as compared with 65 in normal marrow, and the percentage of myelocytes arises to 27 as compared

TABLE 3.—*Percentages of Different Types of Cells Observed in Sternal Marrow in Ten Cases in which Aplastic Anemia was Associated with Active Marrow (Group 3).*

Case	Neutrophils	Myelocytes A	Myelocytes B	Myelocytes C	Myeloblasts	Eosinophils	Basophils	Normoblasts	Erythroblasts, Late	Erythroblasts, Early	Myeloblasts	Clasmatocytes	Megakaryocytes	Monocytes	Primitive	Unclassified
1.....	22.00	3.00	4.20	21.00	0.6	10.00	...	5.40	6.20	9.00	1.8	...	...	...	16.80	...
2.....	1.00	14.00	27.00	36.00	1.6	6.40	...	5.00	0.40	....	...	...	...	...	6.40	...
3.....	36.40	0.80	5.60	22.60	...	0.60	...	24.00	5.20	0.60	...	...	...	...	4.20	...
4.....	26.00	0.60	3.60	23.40	1.0	0.80	...	20.20	16.00	2.00	0.2	...	...	0.2	6.00	1.0
5.....	23.60	1.60	1.80	27.60	4.4	6.60	...	18.60	5.40	0.80	...	...	0.4	...	9.20	...
6.....	9.00	0.40	3.60	18.00	...	3.00	0.4	24.40	12.00	4.30	...	...	...	...	27.00	...
7.....	7.60	0.20	0.60	6.60	6.0	5.20	...	40.80	12.40	2.80	...	0.6	0.2	...	17.00	...
8.....	36.00	....	1.00	3.00	...	1.33	...	46.33	6.33	1.33	...	...	...	...	4.66	...
9.....	12.00	3.00	3.00	7.00	0.4	5.40	...	31.00	8.60	4.40	...	...	...	...	24.00	...
10.....	20.70	0.50	5.50	25.00	...	1.10	0.1	36.20	4.40	2.10	0.1	0.1	...	...	4.20	...
Average.....	19.49	2.41	5.71	19.02	1.4	4.04	...	25.19	7.69	2.73	...	...	...	...	12.00	...
Normal.....	47.80	0.20	2.80	12.60	...	18.00	...	10.80	1.80	....	...	...	...	...	6.00	...

with 15 in normal marrow. The relative numbers of erythroblasts and normoblasts are strikingly increased.

When the marrows of this group are studied in fixed and stained preparations, the suppression of maturation is clearly apparent, although the total number of cells is increased and the general anatomic arrangement of the marrow does not vary greatly from the normal. Few polymorphonuclear leukocytes are present, myelocytes are numerous, and the earlier stages of erythropoiesis are well represented. Photomicrographs of marrows of this group are shown in figure 2 *E* and *F*.

Group 4. Aplastic Anemia with Megakaryocytic Marrow.—Seven marrows showing this condition, 3 of which were studied supravitally, are present in this series. A megakaryocytic replacement of the marrow presenting the clinical picture of primary anemia is so infrequently recognized and so little understood that it warrants special discussion.

Clinically, the condition is marked by extreme leukopenia, granulopenia and the presence of increased numbers of myelocytes and monocytes in the circulating blood. Anemia is slowly progressive, with a slight though definite tendency toward spontaneous remissions. In spite of the severe anemia and granulopenia, there is no thrombopenia, no bleeding and no necrosis of mucous membranes. The last two facts should serve to suggest the diagnosis when the cause of an intractable severe anemia is obscure, particularly when the spleen and liver are palpable or even when peripheral lymph nodes are slightly enlarged.

Histologically, the changes in the marrow are marked and characteristic (fig. 3 *A* and *B*). The normal orderly arrangement of hemopoietic cells is completely obliterated. There is marked proliferation of cells of medium size, with basophilic nuclei and a rather small amount of palely basophilic cytoplasm. Many of these cells have apparently fused to assume the most bizarre shapes, and, although they vary in size, they are in general much larger than any cells which are present in normal marrow except megakaryocytes. Many have developed into what appear to be typical adult megakaryocytes. The nuclei of these cells vary greatly in size and shape, as well as in their content of chromatin. They may at times assume the appearance of the nuclei of tumor giant cells, and many giant cells are present. In 4 of the 7 cases, the biopsy diagnosis has been confirmed by the observations at autopsy. In the remaining 3 cases, tissue removed post mortem is not available, but the lesions in the material removed at operation are so characteristic that little doubt can be entertained as to the diagnosis.

Studied supravitally (tables 4 and 6), the most striking change seen in these marrows is a reduction in the number of polymorphonuclear leukocytes and a very great increase in myelocytes and myeloblasts. Evidence of a failure of maturation to red cells, such as was seen in the hypoplastic or hyperplastic marrows of the patients with aplastic anemia previously described, was not obtained. The great number of abnormal, multinucleated cells seen in the fixed material does not appear in the supravitally stained tissues, since these cells are firmly in contact with other cells and are not expressed in the loose tissue from which the supravital preparations are made. It is inferred that the anemia is due to replacement of erythropoietic tissue by the hemopoietically inactive megakaryocytes and the precursors of the latter rather than to failure of maturation of erythropoietic cells. The failure of leukocytes to mature completely is marked, but the basic change is a metamorphosis and replacement of normal marrow tissue. In 4 cases studied post mortem the blood channels of the liver, spleen and lymph nodes contained numbers of fairly typical megakaryocytes. No dense infiltration of tissue by these cells has been seen, however. From

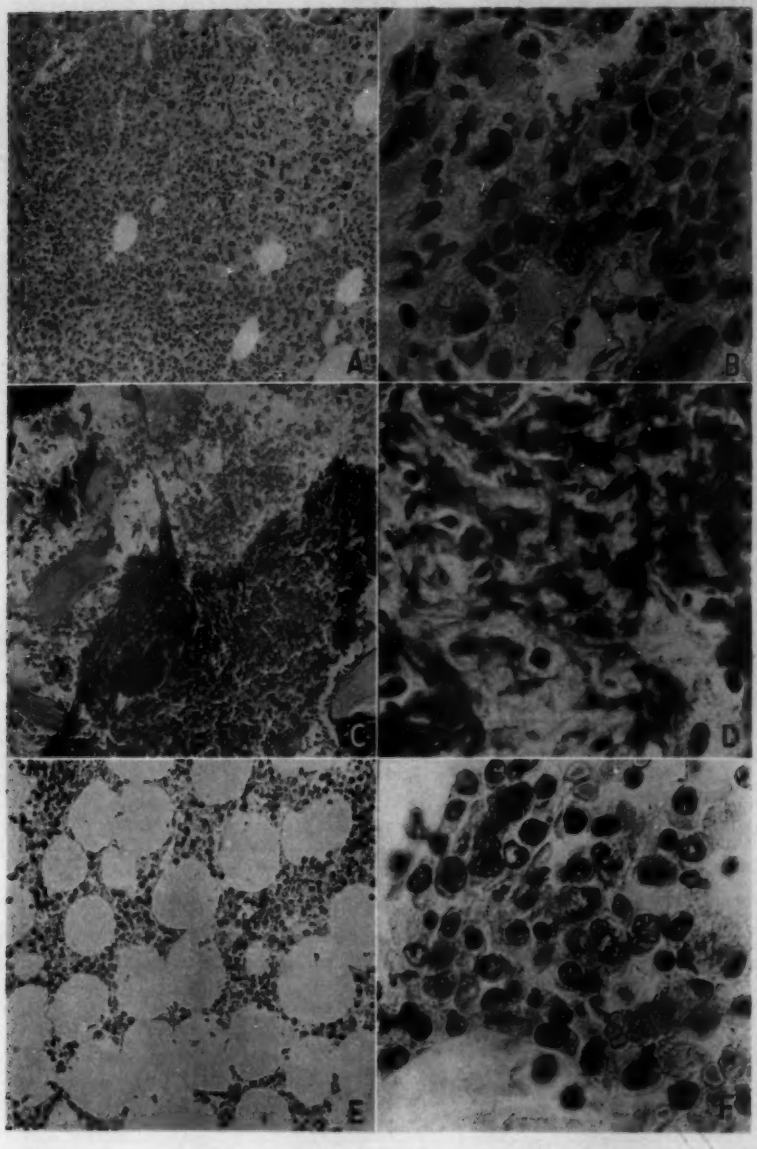

Fig. 3.—*A*, megakaryocytic sternal marrow; × 125. *B*, megakaryocytic sternal marrow; × 500. *C*, sclerotic sternal marrow; × 125. *D*, sclerotic sternal marrow; × 500. *E*, sternal marrow in agranulocytosis; × 125. *F*, sternal marrow in agranulocytosis; × 500.

the massive metaplasia of the bone marrow and from the presence of megakaryocytes in the circulating channels of organs other than the marrow it may be argued that these cases are in fact instances of

TABLE 4.—*Percentages of Different Types of Cells Observed in Sternal Marrow in Three Cases in Which Aplastic Anemia Was Associated with Megakaryocytic Marrow (Group 4).*

Case	Neutrophils	Myelocytes A	Myelocytes B	Myelocytes C	Myeloblasts	Eosinophils	Normoblasts	Erythroblasts, Late	Erythroblasts, Early	Clasmatocytes	Megakaryocytes	Primitive
1.....	18.6	7.0	11.8	35.0	1.8	3.2	2.2	....	....	0.2	....	22.2
2.....	6.0	13.0	19.0	32.0	9.0	....	12.0	4.0	....	....	....	5.0
3.....	30.0	0.4	0.8	15.0	....	15.0	25.4	4.4	0.2	....	0.4	8.6
Average..	18.2	6.8	10.5	27.3	3.6	6.0	13.2	2.8	....	....	....	11.9

TABLE 5.—*Percentages of Different Types of Cells Observed in Sternal Marrow in Seven Cases of Pernicious Anemia.*

Case	Neutrophils	Myelocytes A	Myelocytes B	Myelocytes C	Myeloblasts	Eosinophils	Basophils	Normoblasts	Erythroblasts, Late	Erythroblasts, Early	Megaloblasts	Clasmatocytes	Megakaryocytes	Primitive	Unclassified
1.....	16.40	...	4.00	12.80	...	2.00	0.1	11.10	16.60	10.10	0.70	...	0.1	22.50	3.6
2.....	37.33	...	1.66	9.33	...	6.00	...	8.00	13.66	9.33	....	...	...	14.66	...
3.....	11.00	...	2.33	11.66	...	3.33	...	5.66	12.66	20.00	4.40	...	...	29.00	...
4.....	37.00	2.8	4.80	7.20	...	1.60	...	7.20	6.40	7.20	1.66	...	...	24.20	...
5.....	22.20	0.4	2.40	5.40	...	4.00	...	15.60	15.80	13.40	1.60	0.6	...	12.60	...
6.....	28.70	...	1.10	14.00	...	5.00	...	18.00	14.70	9.50	2.50	...	...	6.50	...
7.....	36.00	0.4	0.60	12.80	0.4	5.20	...	18.60	6.20	6.80	3.20	...	...	6.40	3.4
Average.....	23.80	...	2.40	10.40	...	3.90	...	12.00	12.20	10.00	2.00	...	...	16.50	...

TABLE 6.—*Average Percentages of Different Types of Cells in Sternal Marrow in Different Groups.*

Group	Granulocytes	Myelocytes	Myeloblasts	Normoblasts	Erythroblasts	Primitive Cells
Normal.....	65	15	2	10	2	6
1.....	30	27	..	17	2	27
2.....	13	21	6	12	4	36
3.....	24	27	1	25	10	12
4.....	24	45	3.6	13	3	12
Pernicious anemia.....	28	13	..	12	25	16

aleukemic megakaryocytic leukemia. Since anemia has been the presenting manifestation in our cases, and since at no time was a leukemic blood picture observed, the inclusion of these cases as instances of refractory anemia is considered justified.

Group 5. Aplastic Anemia with Sclerotic Marrow.—Three marrows presenting this condition are present in the series, in not one of which was it possible to obtain a supravital preparation suitable for study. This condition has been reviewed by Chapman,[15] also by Stephens and Bredeck.[16] It is characterized pathologically by a diffuse increase of connective tissue in the marrow, associated with anemia and at times an aleukemic blood picture, perhaps due to compensatory myeloid metaplasia of the spleen. The picture is strikingly characteristic and easily differentiated from other pathologic conditions of the bone marrow. As seen in figure 3 *C* and *D*, the normal structure has been completely replaced by elongated marrow cells, matted together. In 1 of the cases the process was so extensive that bone changes could be demonstrated by roentgen examination. Anemia was the presenting manifestation in the patients; at no time was a leukemic blood picture observed; hence the inclusion of the cases as a group of cases of aplastic anemia is considered justified.

COMMENT

On the basis of the pathologic changes of the bone marrow, the cases of aplastic anemia studied have been divided into five groups. Three of these groups show similar histologic changes and differ from each other principally in the degree of cellularity observed. In all three the basic defect is an absence of mature forms of hemopoietic cells, a change which may be associated with a decrease in cell numbers as in group 1, an apparently normal cellularity as in group 3 or a very great increase in cellularity as in group 2. The fourth group is somewhat different in that, although a defect in maturation is present, the major change is a replacement of hemopoietic marrow by a cellular structure made up of megakaryocytes and their precursors. The fifth group is characterized by an elongation and matting together of the marrow cells.

Since three of the five subgroups present pathologic changes which appear to be fundamentally similar, it may be profitable to inquire into the nature of the change, if possible, by study of an analogous pathologic syndrome in a condition not ordinarily grouped with aplastic anemia. Evidence will be presented in favor of the view that acute agranulocytosis affords such a condition.

As previously mentioned, analysis of the differential counts made on supravitally stained smears of material removed by puncture of the sternal marrow reveals that primitive, undifferentiated cells are present in the marrow in large numbers when a suppression of maturation resulting in aplastic anemia takes place. It accordingly appears that the primitive cells deserve special attention in any consideration of the

15. Chapman, E. M.: Am. J. M. Sc. **185**:171, 1933.
16. Stephens, D. J., and Bredeck, J. F.: Ann. Int. Med. **6**:1087, 1933.

mechanism of the development of aplastic anemia. As previously stated, the exact relationship of these cells to hemopoietic development is not clear. For a detailed discussion of the subject, one may refer to the publications of Cunningham, Sabin and Doan [14] and Sabin and co-workers.[13] In the course of the studies of the first two groups of aplastic anemia, an opportunity was afforded to apply the same histologic methods to the study of the bone marrow in 3 cases of acute agranulocytosis, and strikingly similar pathologic changes were found to be present. Furthermore, the study of the bone marrow in agranulocytosis afforded an opportunity to examine the marrow of man under circumstances which freed the material from the normally confusing hemopoiesis—observations were made similar to those made by Cunningham, Sabin and Doan [14] on the marrows of rabbits rendered granulopenic by injections of typhoid vaccine. Supravital study of human marrow at biopsy in a case of acute agranulocytosis of less then twenty-four hours' duration showed striking variations from normal. No polymorphonuclear cells were seen, though myelocytes were present to the number of 31 per cent. The major change, however, was an increase in the percentage of primitive cells to 57 from a normal of 6. Moreover, this increase was quite comparable to that in the number of primitive cells in the marrow in the classic aplastic and in the hyperplastic (or pluricytopenic) form of aplastic anemia. The suppression of maturation at the stage of the primitive cell is readily perceptible in figure 3 *E* and *F*.

It appears, then, that as far as the predominant cell type is concerned the pathologic change in the bone marrow in at least three subgroups of aplastic anemia is similar to that in the marrow in acute agranulocytosis. Certain objections to this statement may be advanced: It is possible that the primitive cell under discussion is not concerned in erythropoiesis but is really a myeloblast. Opposed to this view is the fact that primitive cells are not present in large numbers in the bone marrow in myelogenous leukemia and are present in profusion in certain instances of aplastic anemia in which granulopoiesis has not been seriously interfered with.

If the primitive cell is erythropoietic as well as granulopoietic, a true pluripotential cell, anemia should be a feature of acute agranulocytosis. This it is not, despite the cessation of hemopoietic maturation that is observable, because, owing to the relatively long life of the erythrocyte, sufficient time for anemia to appear does not elapse before either death or remission takes place. Certain instances of *chronic* agranulocytosis are at hand, however, which show clearly that anemia supervenes if the suppression of maturation of the cells in the bone marrow continues for a sufficiently long time.

A third objection advanced is that, judged morphologically, the cells we have termed primitive are really lymphocytes. Two facts serve to invalidate this supposition. Supravitally studied, the primitive cells of the marrow show none of the staining characteristics of lymphocytes, and as seen in sections they differ from lymphocytes in size and structure.

Evidence is, then, at hand that the marrows of certain subgroups of aplastic anemia are pathologically allied so far as all are marked by suppression of maturation and differ principally in the degree of cellularity. The defect of maturation is similar to that seen in the marrow in acute agranulocytosis. The pathologic similarity is borne out by the occurrence of clinical conditions intermediate between acute agranulocytosis and aplastic anemia. Such a similarity suggests that an etiologic factor common to the two conditions may exist.

SUMMARY

Study of 69 cases of idiopathic progressive anemia (not responding to any known hemopoietic agents) by histologic examination of the sternal marrow revealed five distinct subgroups. One of these included cases in which the marrow showed replacement of hemopoietic tissue by a cellular structure composed of megakaryocytes in various stages of development—a true myelophthisic anemia. The second included cases in which the marrow was sclerotic. The remaining three subgroups were distinguished only by the cellularity of the marrow, which was of three types: aplastic, active and hyperplastic.

The basic change common to all three subgroups was a failure of maturation of hemopoietic cells at an early, undifferentiated stage. Comparison of marrow from persons presenting aplastic anemia with marrows from persons presenting acute agranulocytosis shows in the latter a similar lack of maturation and suggests that aplastic anemia and acute agranulocytosis may have some etiologic factor in common.

INCIDENCE OF MILD DEGREES OF ATROPHY IN THE FASCICULUS GRACILIS

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Interest in the subject of mild nonspecific lesions of the spinal cord was aroused by the appearance of Weigert-stained sections from a 37 year old Mexican man who died of pulmonary tuberculosis. The cord and brain of this subject were selected for the preparation of sets of slides to be used by students of neuroanatomy. The body had been used for demonstrations in the study of gross anatomy and had been carefully dissected by the instructors. Except for extensive pulmonary tuberculosis, no evidence of disease was noted, and while the subject was thin, there was not the extreme emaciation so often seen in those dying of tuberculous infection. Grossly, the spinal cord and brain looked entirely normal.

In view of the original object in mind, the Weigert preparations of the cervical and upper thoracic levels were a source of chagrin. As shown in *A* and *B* in the figure, the appearance of these levels when viewed with the naked eye or under low power magnification ($\times$ 5.6) was that of almost complete degeneration of the fasciculus gracilis. Under high power magnification large numbers of intact and normal-looking fibers were present in this fasciculus, and the only difference between this bundle and the rest of the white matter was in the number of fibers occupying a given amount of space. In the fasciculus gracilis each fiber was surrounded by yellow-staining supporting tissue, while in other tracts the fibers were closely packed together, and supporting tissue was conspicuous only around the larger blood vessels. The lower thoracic, lumbar and sacral levels were at first sight entirely normal, but closer study showed a slight but perceptible lightness of the posterior column, which involved the entire bundle in the lumbosacral enlargement and the medial half of the column in the lower thoracic levels. A perceptible difference in the color of the lateral corticospinal tract in the lumbar region as compared with the rest of the lateral column was observed at a later date. Sections stained with sudan IV revealed the same appearances and no free fat. Nissl types of staining showed normal cellular structure. No evidence of arterio-

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sclerosis or of inflammatory reaction was observed in sections stained with hematoxylin and eosin.

A slight increase in the number of glia cells in the fasciculus gracilis was noted with all nuclear stains. With Weigert preparation all levels of the brain stem were normal. Occasional amyloid bodies were seen in all sections studied. After a survey of the literature and a comparison with a number of other cords, it was felt that the specimen showed evidence of some increase in the amount of subpial collagenous tissue, and it was then recalled that the prosectors often remarked on how much tougher the dissection was than had been anticipated. This doubtful fibrosis was the only additional deviation from the normal.

All the textbooks of anatomy and atlases available were examined, and they invariably pictured the adult posterior column as evenly stained by the Weigert method. On that basis the specimen selected as such could scarcely be considered normal. On the other hand, three modern American textbooks of neuropathology gave no illustration or clue concerning the significance of these possibly pathologic changes. After reading the statements of Weil [1] about the artefacts produced by fixation and staining of supposedly pathologic tissue, the material was carefully considered from that standpoint and compared with other specimens subjected to the same general conditions. It was felt that technical errors would not account for the changes, a belief supported by later observations.

The condition described was studied further by examination of locally available material and by a review of the literature. Both approaches elicited information considered worthy of report.

MATERIAL AND METHOD

In each of 31 cadavers dissected by the class in gross anatomy pieces were taken from either the lower cervical or the upper thoracic levels of the spinal cord. The bodies had been embalmed by injections of a 5 per cent dilution of solution of formaldehyde U. S. P., and were kept in a 1 per cent solution of phenol for various periods of less than one year. The blocks of tissue from the spinal cords were embedded in pyroxylin, and sections from 30 to 50 microns in thickness were stained by Weil's modification of the Weigert technic as given in his textbook. The age, sex and cause of death of each subject were learned from the death certificate after all the sections had been classified as to depth of staining of the fasciculus gracilis as compared with the rest of the white matter. Following this, Weigert-stained sections of the spinal cords of 30 cadavers found in the collection of the late Prof. W. Keiller were studied and classified.

1. Weil, A.: A Textbook of Neuropathology, Philadelphia, Lea & Febiger, 1933.

RESULTS

The 31 cords were classified according to lightness of staining of the fasciculus gracilis as follows: light +, 2 (these were nearly but not quite as light as the original specimen); light, 1; light —, 8; light ——, 2; uniform —, 7; and uniform, 11. These arbitrary categories are in themselves meaningless and subject to a large element of personal choice. What they indicate is that in the series examined there was a gradual, almost imperceptible shift from an obviously lightly stained fasciculus gracilis to one that is with equal certainty stained as darkly as other tracts. The picture as a whole is clear to any one, but the exact order of arrangement within the series is difficult to determine. In the figure, *A* to *H* have been arranged to convey the aforementioned impression in condensed form.

The results obtained from examination of Professor Keiller's specimens were about the same as those obtained in the series recently collected. In 15 of these specimens the posterior column was evenly stained, and in the other 15 specimens various degrees of lightness in the fasciculus gracilis were noted. The most marked examples from his collection are shown in the figure, in *C* and *D*. The specimen shown in *C* was from a 63 year old Negro who died, according to the death certificate, of heart failure. In addition to the poorly stained fasciculus gracilis, there was marked acute leptomeningitis. There seemed to be no direct relationship between the two conditions because the fasciculus gracilis under high power looked exactly like that in *A*; i e., there was a reduction in the number of fibers but no evidence of products of degeneration. The specimen shown in *D*, from Professor Keiller's collection, was the only one of the entire number examined that showed evidence of active degeneration. While the gross appearance of this specimen was closely similar to that of the one initially studied, under the microscope it presented an entirely different picture. The whole fasciculus gracilis was filled with fragmented and swollen myelin sheaths as well as pale-staining globules of broken-down myelin. The specimen was from a 19 year old Negro who died of pulmonary tuberculosis.

E, *F* and *G*, from the recent series, are examples of less marked differential staining of the spinal cord, particularly of the fasciculus gracilis. The specimen shown in *E* was from a 28 year old Mexican man who died of pulmonary tuberculosis. The gracile fasciculus was classed as light. The same appearance to a lesser degree was presented by the lateral corticospinal tract and possibly the dorsal spinocerebellar pathways. The appearance of the latter in the figure should be discounted, however, because the suggestion of a halo around the figure was not seen in the actual specimen. The specimen shown in *F*,

classed as light —, was from a white man whose age was given as 93 and whose death occurred from cardiorenal disease. Little evidence of arteriosclerosis was seen in the sections prepared with the Weigert stain. The specimen shown in *G*, also light —, was from a 37 year old Mexican man. It showed deviation from uniform staining in the lateral as well as in the posterior column. This man's death was due to pulmonary tuberculosis. The specimen shown in *H* was not one of the present series but is pictured here to show uniform staining of the posterior column in the presence of long-standing severe destruction of the ventral horns. The specimen was obtained from a middle-aged Negro who died of pneumonia. The man was extremely crippled and wasted. The skeleton was grossly deformed, and most of the musculature of the limbs and trunk presented gross evidence of atrophy. The cells of the ventral horn in the lumbar region were almost totally destroyed and the column was reduced to series of small cysts. Most of the ventral horn in the thoracic part of the cord had disappeared, and the extent of destruction in the cervical region, which was least affected, is shown in the figure. The terminal picture was thought to be the result of a severe attack of anterior poliomyelitis that occurred many years prior to death, probably in adolescence. In spite of this marked pathologic change, the posterior and lateral white columns were entirely normal throughout the cord. The specimen had the additional control value that it was embalmed in the same manner as the other specimens pictured and remained in the storage tanks for at least a year.

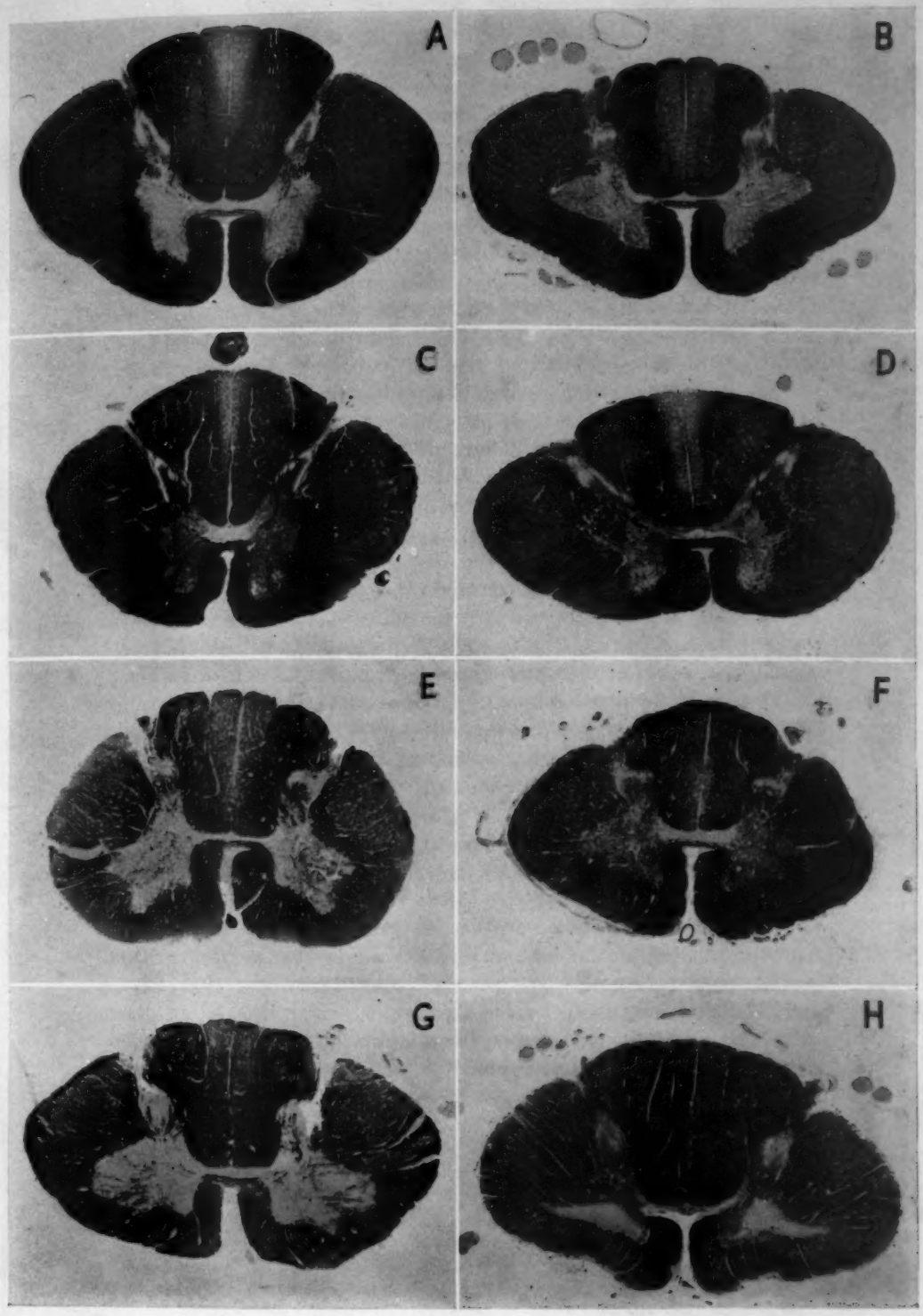
Without counting the questionable specimens, there were 27 of a total of 62 that showed some degree of lightness in the medial part of the posterior column. Eleven of the 27 persons represented were less than 60 years of age, and 6 of these died of pulmonary tuberculosis, 2 of pneumonia, 1 of "acute indigestion," 1 of pellagra and 1 of syphilitic heart disease. The 16 persons who were over 60 years old died of uremia, cerebral hemorrhage or heart disease. Of the 8 persons whose spinal cords showed the most definite change, 5 were found to have died of pulmonary tuberculosis, at ages less than 54 years, and the other 3, of vascular degeneration, at ages well over 60 years.

Unfortunately for the purposes of comparison, the ones whose spinal cords stained uniformly died of the same diseases in about the same proportions. The death certificates for 21 persons whose cords showed uniformly stained posterior columns were located; 4 of these died of pulmonary tuberculosis, 1 of pellagra, 1 of carcinoma of the larynx, 1 of acute alcoholism, 1 of pneumonia and the rest of cardiovascular-renal complications.

The results suggest that a lightly staining fasciculus gracilis is present in about one half of persons over 60 years of age and that it

Explanation of Plate

Sections of the spinal cords from 7 persons; × 5.6. *A*, first cervical level from a 37 year old Mexican man who died of pulmonary tuberculosis. *B*, first thoracic level of the same spinal cord as *A*. *C*, first cervical level from a 63 year old Negro who died of heart disease. *D*, first cervical level from a 19 year old Negro whose death was due to pulmonary tuberculosis. *E*, lower cervical level from a 28 year old Mexican man who died of pulmonary tuberculosis. *F*, first thoracic level from a 93 year old white man whose death resulted from cardiorenal disease. *G*, lower cervical level from a 38 year old Mexican man who died of pulmonary tuberculosis. *H*, lower cervical level from a middle-aged Negro whose death resulted from pneumonia. In general, the figures illustrate the gradual shift in the posterior columns observed from that in which the fasciculous gracilis was very lightly stained to that in which the staining was entirely uniform.


A
B
C
D
E
F
G
H

is frequently observed in younger persons dying of pulmonary tuberculosis. Of 10 persons with pulmonary tuberculosis, the change was seen in 6 and was marked in 5.

COMMENT

As previously mentioned, no photograph of a nonuniformly stained posterior column could be found in a textbook of anatomy or an atlas. When the source of the material used is given, it is invariably found to have been a young adult or an adolescent. The statement of Bruce [2] in the preface of his atlas to the effect that the spinal cord used was from an 18 year old girl and was the only one of 5 selected that met all requirements of normality is probably an index of the difficulty of obtaining material free from pathologic alteration from adults. The present results suggest that failure of the posterior column to stain uniformly is one of the most common and obvious of these difficulties.

Mild degenerative changes in the posterior column, particularly in the medial portion of the cervical region, are described by Buzzard and Greenfield [3] as occurring in pellagra, ergotism, beriberi and lathyrism. Figures 32*b* and 68 in their textbook show lightly staining fasciculi graciles. Figure 32*b* illustrates definite degeneration of one corticospinal tract, and in figure 68, representing a case of lathyrism, partial destruction of the anterior and lateral columns is also indicated.

Turning to the original literature, one is confronted with a scattered and bewildering array of descriptions that include mention of partial degeneration of the posterior column in connection with the neuropathologic changes in a large number of distinct clinical conditions. In fact, the literature has been previously summarized by Woltman,[4] who stated that chronic degeneration of the nervous system (including change in the posterior columns) may be concomitant with almost any chronic intoxication. He listed fifteen different causative conditions, including all of those cited further on in this paper. Without pretence of making a complete survey, I shall in the succeeding paragraphs briefly mention some of the papers in which changes are described similar to those seen in the routine examination of cadavers.

Diabetes mellitus is sometimes associated with severe, active degeneration of the lateral and particularly of the medial part of the posterior column. Such was the case of the specimen recently described by Griggs and Olsen.[5] However, many cadavers in which diabetes was

2. Bruce, A.: A Topographical Atlas of the Spinal Cord, London, Williams & Norgate, 1901.

3. Buzzard, E. F., and Greenfield, J. G.: Pathology of the Nervous System, New York, Paul B. Hoeber, 1923.

4. Woltman, H. W.: Am. J. M. Sc. **157**:400, 1919.

5. Griggs, D. E., and Olsen, C. W.: Arch. Neurol. & Psychiat. **38**:564, 1937.

the primary cause of death have been examined without finding such definite pathologic changes as were reported by Griggs and Olsen. From a review of the literature and 2 cases of their own, Woltman and Wilder [6] concluded that the changes in the spinal cord found in diabetic persons could be attributed to senility and arteriosclerosis. These authors did not specifically state what the alterations observed in their own cases were. Referring to some of the original papers reviewed by Woltman and Wilder, one finds chiefly descriptions of changes essentially the same as those recorded here. Williamson [7a] reported 2 cases of diabetes in which the lesions in the spinal cord were limited to mild changes in the column of Goll. Both of the patients had extensive pulmonary tuberculosis. Three others examined had normal cords and no tuberculosis. Later Williamson [7b] described an additional case, that of a man aged 25 who had pulmonary tuberculosis in an early stage in addition to diabetes. The cord changes noted were a slight excess of glia in Goll's column, some diminution in the number and size of the fibers in this column and occasional swollen axis-cylinders. Marchi's method showed black granules throughout the posterior column, most marked in the cervical region and in the zone of the intramedullary roots. Results with Marchi's method published without figures or references to the difficulties of the method should be considered doubtful evidence of recent degeneration. Such is the situation in Williamson's descriptions. On the other hand, the changes noted by Sandmeyer [8] with the Marchi method were, if one may judge from the figures and his account of the technic, undoubtedly true degeneration. Sandmeyer's patient was a 9 year old girl, and the lesion was limited to the region adjacent to the posterior septum, particularly in the cervical segments. Nonne [9] reported a case of diabetes in a woman dying at the age of 63. The chief lesion of the spinal cord was degeneration of the cells of the anterior horn, but slight rarefaction of all three funiculi was seen in sections prepared by the Weigert method. Schweiger [10] reported 3 cases of diabetes in which he observed rarefaction of the posterior columns throughout, most marked in the column of Goll, mild gliosis in the affected regions and a minimal Marchi reaction. In a fourth case in which there were marked nervous symptoms and concomitant tuberculosis, he found the spinal cord normal and therefore considered the condition to be peripheral neuritis. Schweiger commented on the complicating factors of tuberculosis and syphilis. Of the 39 cases reviewed by Woltman

6. Woltman, H. W., and Wilder, R. M.: Arch. Int. Med. **44**:576, 1929.
7. Williamson, R. T.: (*a*) Brit. M. J. **1**:398, 1894; (*b*) **1**:122, 1904.
8. Sandmeyer, W.: Deutsches Arch. f. klin. Med. **50**:381, 1892.
9. Nonne, M.: Berl. klin. Wchnschr. **33**:206, 1896.
10. Schweiger, L.: Arb. a. d. neurol. Inst. a. d. Wien. Univ. **14**:39, 1908.

and Wilder [6] in which the spinal cords were examined, minor changes in the posterior columns were noted in 15, and in most of these the pathologic changes were limited to that area. In 7 of these cases there was severe pulmonary tuberculosis in addition to the diabetes. In an additional case in which the cord showed lesions without change in the posterior column there was also tuberculosis. Of the other 8 cases in which examination of the cord gave positive results, 5 concerned persons over 50 years of age, 1 a child aged 9 and 1 a person aged 26, who also had syphilis. In the remaining case the age was not given.

The literature on neuropathologic observations in pellagra contains numerous references to degenerative changes in the posterior columns, often associated with similar changes in the lateral columns. Sandwith [11] described the spinal cords from 3 persons who died of pellagra. One cord was normal, 1 was apparently exactly like that described in the introduction of the present paper, and in the third the degeneration was much more severe. Wilson [12] also described loss of fibers in cases of pellagra. This loss was not systematized but was most marked in the posterior columnn; the losses varied from light to severe; most specimens showed signs of active degeneration. Singer and Pollock [13] examined the spinal cords from 15 persons and found some loss of staining of Goll's column in all of them. In most instances the lightened area was in the center of the column, bordering the midline. Under high power the majority of the fibers were well stained, but scattered fibers looked degenerated. The lesion was most marked in the cervical region and in some instances was entirely absent from the lumbar and dorsal regions. Again this description might well apply to many of the spinal cords from the cadavers under discussion. Langworthy [14] described the spinal cord from a person with pellagra, in which similar changes were limited to the lateral column. The change described approximated what is seen in the lateral columns shown in *F* and *G*, in the figure. In Langworthy's case there also was present pulmonary tuberculosis, and he raised the question as to which disease was responsible for the changes noted in the spinal cord.

Winkelman's [15] review of the neuropathology of pellagra was not available locally but is quoted by Orton and Bender [16] as giving chronic

11. Sandwith, F. M.: J. Path. & Bact. **7**:460, 1901.
12. Wilson, S. A. K.: Proc. Roy. Soc. Med. **7**:31, 1914.
13. Singer, D., and Pollock, L. J.: Arch. Int. Med. **11**:555, 1913.
14. Langworthy, O.: Brain **54**:291, 1931.
15. Winkelman, N. W.: Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:38, 1926; cited by Orton and Bender.[16]
16. Orton, S. T., and Bender, L.: Bull. Neurol. Inst. New York **1**:506, 1931.

scleroses of the lateral and posterior columns a prominent place among the findings in this disease.

In some cases [17] in which the disease observed was considered a form of hereditary ataxia, the pathologic changes were limited to mild degenerative changes in the column of Goll in the cervical region and even more questionable changes in the dorsal spinocerebellar tract. Both of the patients died of tuberculosis.

Likewise changes of this same type have been described in non-pernicious forms of anemia—for instance, the case reported by Clarke [18] of a man dying of pneumonia at the age of 28. The subject suffered from severe anemia for three and a half years and was then healthy for two years prior to death. The nervous symptoms were persistent numbness and tingling of the feet. The only alteration found in the spinal cord was a loss of fibers in the cervical region of Goll's column, demonstrated by the Weigert method. The Marchi reaction was negative.

Among other changes in chronic alcoholism, Bender [19] noted diminution in the number of nerve fibers in the posterior and lateral columns. The observation is explained on the basis of the blood supply.

In spite of the number of cases cited in which pulmonary tuberculosis was a complicating factor and the apparent frequency with which alteration of the posterior column is associated with that disease in the present series, papers describing such changes in uncomplicated tuberculous infection are not numerous. Three cases in which this association was observed were mentioned by Lichtheim [20] and additional ones by Sand.[21] Davison and Keschner [22] stated that tuberculosis is one of the causes of subacute toxic degeneration of the spinal cord giving clinical symptoms of myelitis. Ide [23] found that the sciatic nerves, both fibers and supporting tissue, were smaller in tuberculous cadavers than in those in which death was due to other conditions, and therefore a parallel change might be expected in the posterior columns.

According to Weil and Kraus,[24] the earlier reports of changes in the spinal cord, including loss of fibers in the posterior column, as a result of the cachexia of cancer are of small consequence after

17. Klippel, M., and Durante, G.: Rev. de méd., Paris **7**:467, 1892. Meyer, A., and Brown, S.: Brain **20**:267, 1897.
18. Clarke, J. M.: Brain **27**:441, 1904.
19. Bender, L.: Arch. Neurol. & Psychiat. **31**:310, 1934.
20. Lichtheim: Tagebl. d. Versamml. deutsch. Naturf. u. Aerzte **62**:419, 1889.
21. Sand, R.: Bull. Acad. roy. de méd. de Belgique **17**:693, 1903.
22. Davison, C., and Keschner, M.: Arch. Neurol. & Psychiat. **29**:600, 1933.
23. Ide, H.: J. Comp. Neurol. **51**:457, 1930.
24. Weil, A., and Kraus, W. M.: Am. J. M. Sc. **171**:825, 1926.

metastasis and syphilis are ruled out. These authors reported a total of 19 cases in which cancer was of long duration and cachexia was severe. In 9 of the cases the spinal cord was normal; in 4 the changes in the cord were attributed to metastasis, and in 3 the changes noted were said to be due to syphilis or to arteriosclerosis. Weil and Kraus mentioned 3 cases in which the changes in the spinal cord were limited to slight diminution in the number of fibers in the posterior column, beginning in the lumbar region. Two of these cords were regarded as arteriosclerotic, and the other was evidently considered normal.

Thinning of the fasciculus gracilis as a normal change with increase in age is to be expected from anatomic studies pointing to gradual dissolution of the nervous system with advance in age. This senile degeneration has been more or less accurately determined for several parts of the nervous system by various observers. Normal degeneration in peripheral nerves was first carefully described by Mayer [25] for all classes of vertebrates. Later the same finding in man was reported by Teuscher.[26] Teuscher's figures gathered from persons dying of pulmonary tuberculosis and carcinoma, when compared with Duncan's [27] figures from persons dying suddenly, indicate clearly the increased rate of destruction of neurons occasioned by toxic and wasting conditions. This result was supported by Duncan's observations on normal and diseased rats. Stern [28] found approximately a 30 per cent loss of area in the posterior columns between the third and ninth decades. Recently Corbin and Gardner [29] noted a similar loss in the number of dorsal root fibers of the thoracic regions. Decreases in number of the same order have been noted in the Purkinje cells of the cerebellum of man by Ellis [30] and in that of the rat by Inukai.[31] The same loss for the ventral roots of small mammals was demonstrated by Duncan.[32]

The literature cited implies that uniformity of staining is the index of normality in a Weigert preparation. With such a definition in mind, it follows that nearly one half of the spinal cords from 62 cadavers were abnormal in this respect.

Evidence of loss of fibers in the fasciculus gracilis in persons over 60 years of age might be considered as a change of old age reflecting the known normal loss of nerve cells throughout life, or it might

25. Mayer, S.: Ztschr. f. Heilk. **2**:154, 1881.
26. Teuscher, P.: Arch. f. mikr. Anat. **36**:579, 1890.
27. Duncan, D.: J. Comp. Neurol. **51**:197, 1930.
28. Stern, R.: Arb. a. d. neurol. Inst. a. d. Wien. Univ. **14**:329, 1928.
29. Corbin, K. B., and Gardner, E. D.: Anat. Rec. **68**:63, 1937.
30. Ellis, R. S.: J. Comp. Neurol. **32**:1, 1920.
31. Inukai, T.: J. Comp. Neurol. **45**:1, 1928.
32. Duncan, D.: J. Comp. Neurol. **59**:47, 1934.

be attributed to arteriosclerosis as suggested by Woltman,[33] Weil and Kraus, Bender and others, although vascular degeneration was not striking in the Weigert preparations examined. The possibilities of syphilis and malnutrition occurring at some earlier period in life must be borne in mind. In other words, there is evidence of partial atrophy of the fasciculus gracilis in many persons over 60, but the etiologic background of the condition is unknown.

The finding of a lightly staining fasciculus gracilis in over one half of the cases of pulmonary tuberculosis examined and the observation of acute degeneration of the bundle in one are strongly suggestive of a specific effect of this disease on nervous tissue. A considerable body of literature is quoted to the same effect. Here likewise the question as to whether it is due to an acceleration of the aging process or to some more definite mechanism is unanswered.

The clinical histories of the persons whose spinal cords were examined are not available, so nothing is known as to what, if any, symptoms the recorded changes were associated with. Most likely any symptoms present would have been so slight as to escape the ordinary means of detection. However, the recent work of Newman and Corbin [34] on individual and age variations in vibratory acuity and the careful studies of Woltman [33] on the cord symptoms in arteriosclerosis of the central nervous system suggest that the changes observed were accompanied by discernible subjective and objective symptoms.

SUMMARY

Examination of Weigert-stained sections of the spinal cords from 62 cadavers demonstrated that a pale-staining fasciculus gracilis is not uncommon. In 8 of the specimens the difference in color between the fasciculus gracilis and the fasciculus cuneatus was striking, and in 21 additional specimens the difference between the two fasciculi was detectable. The other specimens showed uniform staining of the entire posterior column.

The appearances noted are regarded as evidence of loss of nerve fibers and were more frequent and marked in the spinal cords of persons who died of pulmonary tuberculosis.

33. Woltman, H. W.: M. Clin. North America **5**:511, 1921.

34. Newman, H. W., and Corbin, K. B.: Proc. Soc. Exper. Biol. & Med. **35**: 273, 1936.

SYSTEMIC PROLIFERATION OF THE RETICULO-ENDOTHELIAL SYSTEM (RETICULO-ENDOTHELIOSIS)

REPORT OF A CASE AND COMMENTS ON THE LITERATURE

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The manifold potentialities of the reticuloendothelial system have of late aroused marked interest among pathologists and clinicians. It has been fairly well established that the widespread elements of this system are intimately related to the important physiologic functions of hemoglobin and iron metabolism, intermediate lipoid metabolism and the formation of antibodies. The active phagocytic power of the tissue histiocytes has long been demonstrated and is listed among the important phenomena of inflammation. Based on these physiologic foundations, a wide variety of clinical entities have been recognized as implicating these cells. Though apparently widely separated clinically, many of these dyscrasias are fundamentally similar because of the involvement of identical functions. The diversity of disease pictures prompted Epstein [1] in 1925 to attempt to classify the generalized alterations of the reticuloendothelial system under the generic term "histiocytomatoses." He listed them as follows:

(*a*) Disturbances of the function of storage. These include the so-called lipoidoses: Gaucher's disease, Niemann-Pick disease and Hand-Schüller-Christian disease.

(*b*) Infectious proliferative granuloma. Hodgkin's disease is given as an example.

(*c*) Hyperplasia. Monocytic leukemia of the leukemic and aleukemic varieties are included here.

(*d*) Dysplasia. This covers the so-called reticuloma and the endothelioma.

This classification does not take into account the well known proliferation of reticuloendothelial elements called forth by such specific infections as tuberculosis, typhoid fever, kala-azar, syphilis and undulant fever. It is true that in the latter group there may or may not be systemic hyperplasia. In this paper, however, I wish to report an

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1. Epstein, E.: Med. Klin. **21**:1501, 1925.

infrequently encountered type of systemic proliferation of the reticuloendothelial apparatus, i. e., the so-called reticuloendotheliosis. I wish further to discuss the somewhat ill defined relationship of this condition to other systemic disturbances of this group of cells which are included in the latter three groups of Epstein's classification.

ANATOMY AND PHYSIOLOGY

A clearcut conception of the anatomic changes produced by proliferation of the cells of the reticuloendothelial system can be attained best by a primary consideration of the anatomic data. The first component of this peripatetic system to attract attention was the cell designated by Ranvier [2] as the clasmatocyte. He described phagocytosis by certain connective tissue elements which were distinct from the ordinary fibroblasts. These phagocytic cells were studied by numerous investigators, each of whom applied a different name to them. In this way, they came to be known variously as macrophages (Metchnikoff), adventitial cells (Marchand), resting wandering cells and polyblasts (Maximow). It was Metchnikoff, in particular, who described the important role of these cells in inflammation, with their ability to phagocytose pathogenic bacteria and the remnants of dead cells. Ribbert [3] noted that these cells selectively picked up colloidal suspensions of saccharated ferric oxide N.F. and lithium carmine injected intravitally. The application of newer technics of vital staining with colloidal solutions of acid aniline dyes by Goldmann [4] and Tsaschin,[5] in 1909 and 1913, respectively, brought about an extension of the conception of this group of cells. Accumulation of dye particles was noted not only in the macrophages of the common diffuse connective tissue but in other cells distributed widely over the body. The most intense coloration was present in the spleen, liver, lymph nodes and bone marrow. Maximow [6] stated that "in all these tissues the ability of certain cells to store colloidal dyes and to phagocytose appears to be combined with their tendency to become mobilized, to transform themselves into free ameboid cells, giant cells, epithelioid cells, etc." Aschoff and Kiyono,[7] in 1913, introduced the term "histiocyte" to designate this mesenchymal mononuclear phagocyte and popularized the concept of a reticuloendothelial system. In this system the following cell types, then, are included: the histiocytes of the connective tissue and of the serous membranes; the reticular cells

2. Ranvier, L.: Compt. rend. Acad. d. sc. **110**:165, 1890.

3. Ribbert, H.: Ztschr. f. allg. Physiol. **4**:201, 1904.

4. Goldmann, E. E.: Beitr. z. klin. Chir. **64**:192, 1909.

5. Tsaschin, S.: Folia haemat. **17**:318, 1913.

6. Maximow, A. A.: The Macrophages or Histiocytes, in Cowdry, E. V.: Special Cytology, New York, Paul B. Hoeber, Inc., 1932, vol. 11, p. 711.

7. Aschoff, L., and Kiyono, K.: Folia haemat. **15**:383, 1913.

of the lymphoid and myeloid tissues and of the red pulp of the spleen; the squamous cells lining the lymph sinuses in the lymph nodes and the venous sinuses in the bone marrow and spleen; the Kupffer cells of the hepatic capillaries and some of the cells in the walls of the venous capillaries of the adrenals and pituitary. The squamous or endothelial cells have been designated as littoral cells by Maximow to distinguish them from the ordinary vascular endothelium.

In view of the intimate relationship of this group of cells to the hemopoietic system, a brief reference to their association with the monocyte of the circulating blood seems not amiss. This extremely controversial subject has been the object of a great many investigations. Forkner,[8] writing in 1932, was able to list nineteen separate views. In general, there are three schools of opinion: those who believe the monocyte to originate from the lymphocyte (Maximow;[9] Bloom[10]); those who believe in an origin from the myeloblast (Naegeli;[11] Piney[12]), and those who believe the cell to be of reticuloendothelial origin (Aschoff and Kiyono;[7] Doan, Cunningham and Sabin[13]). The majority of opinions today distinctly favor the latter view. In support of this are numerous data of a tissue-cultural, bacteriologic and pathologic nature (Murray, Webb and Swann;[14] Sabin[15] and others).

THE LITERATURE

Systemic proliferation of the reticuloendothelial system is known to occur in a variety of distinct clinical entities. Exclusive of the lipoid metabolic disturbances, there is a large group of diseases, including Hodgkin's disease, monocytic leukemia and reticuloendothelioma, which often produce systemic disturbances of this apparatus and have sometimes been referred to collectively as reticuloendothelioses. It seems feasible now, with the increased data available, to limit the use of this term to a group of cases which are emerging more clearly as additional reports appear in the literature. Reticuloendotheliosis, as presented in this paper, may be defined as a systemic proliferation of the system

8. Forkner, C. E.: Arch. Int. Med. **53**:1, 1934.

9. Maximow, A. A.: The Lymphocytes and Plasma Cells, in Cowdry, E. V.: Special Cytology, New York, Paul B. Hoeber, Inc., 1932, vol. 11, p. 601.

10. Bloom, W.: Folia haemat. **37**:1, 1928.

11. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 5, Berlin, Julius Springer, 1931.

12. Piney, A.: Recent Advances in Hematology, ed. 3, London, J. & A. Churchill, Ltd., 1931.

13. Doan, C. A.; Cunningham, R. S., and Sabin, F. R.: Contrib. Embryol. **16**:125, 1925.

14. Murray, E. G. D.; Webb, R. A., and Swann, M. B. R.: J. Path. & Bact. **29**:407, 1926.

15. Sabin, F. R.: Physiol. Rev. **12**:141, 1932.

of histiocytes, unassociated with any demonstrable metabolic disturbance and apparently occupying an intermediate position between inflammatory hyperplasia and malignant neoplasia. For the purpose of clarifying the position of this entity I shall diverge somewhat from Epstein's classification and attempt to reallocate the aforementioned types of dyscrasia on a morphologic and clinical basis.

One may divide cases of systemic retothelial proliferation into three large groups: (*a*) monocytic leukemic, with or without local invasive neoplastic growth; (*b*) retothelial sarcoma; (*c*) reticuloendotheliosis. Because of the obscurity of the etiologic factors, this type of classification, with emphasis placed on morphologic differences, appears to be more useful clinically than other types. The position of Hodgkin's disease will be referred to later. Because of the intimate relationship of the aforementioned entities, overlapping of their narrow and artificial boundaries occurs, but typical examples of each may be distinguished both clinically and pathologically.

Monocytic leukemia is becoming firmly established as a third form of leukemia and is occasionally referred to as leukemic reticuloendotheliosis. In reviewing the literature recently, Osgood [15a] noted that of 532 cases of leukemia, the monocytic variety constituted approximately 5.1 per cent. Acute, subacute and chronic varieties have been reported, the acute being overwhelmingly more frequent. An aleukemic picture is fairly common. Pathologically, monocytic leukemia is usually characterized by diffuse monocytic infiltration of the tissues associated with systemic reticuloendothelial hyperplasia. A type of case is seen, however, in which leukemic monocytosis is accompanied by the tissue changes characteristic of myelosis. This has been referred to by Gittins and Hawksley,[16] Wainwright and Duff,[17] and Campbell, Henderson and Croom,[18] among others. The latter authors suggested that in monocytic leukemia there occurs stimulation of a common stem cell with simultaneous differentiation into two distinct daughter types. The occurrence of cases of this type continues to jeopardize those views which uphold the independent origin of the monocyte.

As a variant of the simple leukemic picture, one encounters in some instances local tumor formation associated with this dyscrasia. Such neoplasms have been described as occurring in a wide variety of locations by several groups of investigators. The nomenclature in these cases has varied with the whim of the individual reporter. Gittins and

15a. Osgood, E. E.: Arch. Int. Med. **59**:931, 1937.

16. Gittins, R., and Hawksley, J. C.: Arch. Dis. Childhood **8**:241, 1933.

17. Wainwright, C. W., and Duff, G. L.: Bull. Johns Hopkins Hosp. **58**:267, 1936.

18. Campbell, A. C. P.; Henderson, J. L., and Croom, J. H.: J. Path. & Bact. **42**:617, 1936.

Hawksley [19] described in an 11 month old infant an ovarian "endothelioma" which was associated with monocytic leukemia. Mitchell [20] described the case of a 63 year old man who presented subcutaneous nodules subsequently associated with definite leukemia. To this case he applied the term "malignant monoblastoma." Gump [21] and others presented the case of a man aged 55 years who, in addition to definite leukemia, displayed tumors of both orbits, resulting in bilateral exophthalmos. They termed this a case of "monocytic chloroma." Using the term "leukemic sinus reticulosis," Haining, Kimball and Janes [22] reported a case of monocytic leukemia associated with a rectal tumor mass. Campbell, Henderson and Croom [18] described a localized neoplastic mass about the cecum associated with this blood dyscrasia. The paucity of reports of such cases in the literature will undoubtedly be altered with increasing recognition of monocytic leukemia. This entity is apparently analogous to the chloroma and leukosarcoma of the long-established lymphoid and myeloid types of leukemia.

Malignant proliferation of a part or of all of the reticuloendothelial system constitutes a second fairly well defined category in this morphologic classification. The reticulum, or large cell, type of lymphosarcoma, has long been recognized as involving a component of this system. In recent years the term "retothelial sarcoma," introduced by Roulet,[23] has been used to designate a tumor arising in lymph nodes, spleen, bone marrow and occasionally the submucosa of the respiratory or of the gastrointestinal tract. This tumor is the result of malignant proliferation of reticuloendothelial cells of varying degrees of maturity and is characterized by proliferation of argyrophilic reticulum. Widespread malignant change of these cells, constituting virtually a systemic involvement, have been described as retothelial sarcomatosis. Roulet [23] further noted the occasional association of a neoplasm of this type with a leukemoid blood picture of the lymphoid or monocytic type or even with Hodgkin's disease.

A third group of cases which may be culled from the literature appears to occupy an intermediate position between the two already described. No uniformity of opinion exists concerning the nature of these cases. One finds the opinion expressed that they are instances of atypical forms of leukemia, that they are instances of neoplastic growth or that they represent a low grade bacterial or toxic stimulation of the reticuloendothelial system. Examples of this entity, which I

19. Gittins, R., and Hawksley, J. C.: J. Path. & Bact. **36**:115, 1933.

20. Mitchell, L. A.: Malignant Monoblastoma, Ann. Int. Med. **8**:1387, 1935.

21. Gump, M. E.; Hester, E. G., and Lohr, O. W.: Arch. Ophth. **16**:931, 1936.

22. Haining, R. B.; Kimball, T. S., and Janes, O. W.: Arch. Int. Med. **55**: 574, 1935.

23. Roulet, F.: Virchows Arch. f. path. Anat. **286**:702, 1932.

shall refer to hereafter as reticuloendotheliosis, have been described in both children and adults. To Borissowa [24] goes the credit of describing the first cases of reticuloendotheliosis. She, however, described them as examples of Banti's syndrome in an early stage. Letterer,[25] in 1924, first clearly described a disease which he called "aleukemic reticulosis," occurring in children. It was characterized clinically by splenomegaly, hepatomegaly, anemia and purpura and pathologically by diffuse hyperplasia of the reticuloendothelial system to the point of actual replacement of the normal structure in the organs involved. Since that time reports of isolated cases and several reviews of cases have appeared in the literature. Goldzieher and Hornick [26] described what was apparently the first case to be recorded in the American literature under the title "Reticulosis." Dameshek [27] was able to list 13 reasonably well described cases of this entity. Foot and Olcott [28] reported a case under the name of nonlipoid histiocytosis, thus attempting to indicate its close relationship to Niemann-Pick disease (lipoid histiocytosis). Van Creveld and ter Poorten [29] presented a case titled "infective reticulo-endotheliosis" and in reviewing the literature were able to collect 16 other examples. Abt and Denenholz,[30] in reporting a case, chose to denote the condition as Letterer-Siwe disease. Recently, Ritchie and Meyer [31] added a well described case. I do not propose to review exhaustively again the accumulating literature but will attempt to correlate this form of systemic hyperplasia with the others discussed here and to stress the essential unity of cases, irrespective of the age of the patients, within this group. As an aid in doing so I shall present later a case which apparently falls into this category.

CLINICAL PICTURE

The clinical syndrome of reticuloendotheliosis is poorly defined and possesses no pathognomonic characteristics. Cases occur over a broad age period, from 11 days to 75 years. The majority of cases, however, are met with in infants and young children. In the group collected by van Creveld and ter Poorten, who limited themselves to cases in children, the average age was approximately 1½ years. Both sexes are involved with equal regularity. The onset may be described as insidious. Often a history of some recent infection, such as the common cold, grip, otitis

24. Borissowa, A.: Virchows Arch. f. path. Anat. **172**:108, 1903.
25. Letterer, E.: Frankfurt. Ztschr. f. Path. **30**:377, 1924.
26. Goldzieher, M. A., and Hornick, O. S.: Arch. Path. **12**:773, 1931.
27. Dameshek, W.: Folia haemat. **49**:64, 1933.
28. Foot, N. C., and Olcott, C. T.: Am. J. Path. **10**:81, 1934.
29. van Creveld, S., and ter Poorten, F. H.: Arch. Dis. Childhood **10**:125, 1935.
30. Abt, A. F., and Denenholz, E. J.: Am. J. Dis. Child. **51**:499, 1936.
31. Ritchie, G., and Meyer, O. O.: Arch. Path. **22**:729, 1936.

media, tonsillitis or gastrointestinal or even genitourinary infection, may be obtained. The presenting complaints are variable, but perhaps the most frequent is "weakness and fever." The occurrence of repeated attacks of epistaxis, which may be familial, is often noted. Additional evidences of a hemorrhagic diathesis are often manifested, especially in children, in the form of a generalized purpuric and petechial eruption. Fever of a moderate degree is present in most cases but is usually not distinctive. Dameshek, however, reported an undulating type of fever in his case, suggestive of the Pel-Ebstein variety seen in Hodgkin's disease. The total duration of illness is variable; in the series collected by van Creveld and ter Poorten there were cases in which the disease lasted for from four days to twenty-two months; the average duration in their series was approximately three and a half months. All cases reported have had a fatal issue.

Physical examination yields few striking findings. Perhaps the most constant are generalized but variable lymphadenopathy, moderate splenomegaly and hepatomegaly. The lymph nodes are enlarged, usually discrete and not tender. The occurrence of a purpuric or petechial eruption, as already noted, has often led to a diagnosis of thrombopenic purpura. In the case reported by Abt and Denenholz there was a tumor mass localized in the temporal region of the skull. These authors stated that such neoplasms are occasionally present about bones but are usually detected only by roentgen examination.

In a consideration of the laboratory data in the reported cases, one observes that three types of procedures are likely to offer the most help: hematologic, roentgenologic and pathologic. The information offered by the latter type of investigation is usually secured by examination of a lymph node or of a biopsy specimen of bone marrow and will be considered more fully later. There is usually moderate to severe hypochromic anemia, and the leukocyte count is normal or reduced. The differential count may or may not reveal a deviation from normal. Of the 13 cases collected by Dameshek, a slight but significant monocytosis was present in 6. Platelet counts are not mentioned in all cases but, when given, are not consistently lowered. Distinct thrombopenia, however, was a feature of 7 reported cases. It may be stated that when the condition is fully developed one will find a reduction in the relative numbers of all formed elements of the blood, giving rise to a destructive or so-called myelophthisic type of picture. Other data on the blood are not significant.

Roentgen examination of the bony skeleton often yields interesting information. Bony changes were present in 5 cases examined roentgenologically, and I am in agreement with Foot and Olcott, who stated that these findings would have been mentioned more commonly if looked for more frequently. Areas of rarefaction and even of cyst formation

are noted. Such areas have been seen in the pelvis, femurs, vertebrae, skull, humeri and ribs. Goldzieher and Hornick reported a mottled appearance of the bones in their case. In Foot and Olcott's case there were cysts in the intervertebral cartilages and kyphosis clinically. Numerous membranous defects in the skull were present in the case described by van Creveld and ter Poorten. These defects increased to such an extent that the roentgenogram showed a maplike skull. All of these changes can be adequately explained by the histologic changes in the bone marrow.

PATHOLOGY

As reticuloendotheliosis is characterized by systemic proliferation of all elements of the reticuloendothelial system, the most striking changes are present in the spleen, lymph nodes, liver and bone marrow. More rarely there have been noted changes in the lungs, skin, thymus, tonsils and lymph follicles of the intestines. A variable generalized lymphadenopathy is usually present, and one often observes chains of nodes —for example, the cervical or the retroperitoneal—involved as a group. Often, the predominance of one chain is noted. The nodes are usually discrete, and the lesions appear to have no locally invasive tendencies. The consistency of the nodes is normal, and they display a grayish pink or grayish yellow granular cut surface. Splenomegaly is the rule, the organ retaining its normal shape but being of somewhat firmer consistency than is normal. A cross section of this organ shows indistinctness of the usual markings, and in their place one may observe scattered indefinite grayish yellow nodules considerably larger than malpighian bodies. Hepatomegaly is usually present, and one may note here, also, the presence of grayish yellow nodules of varying sizes, scattered through the parenchyma. The organ may occasionally present a fatty appearance, especially in children. On cross section there may be an accentuation of the normal lobular markings, due to cellular infiltration in the sinusoids. The bone marrow is invariably involved, but no uniform description of the gross appearance is encountered in the literature. Some observers have described it as being paler than normal, others as being hard, white and brittle, and still others as being composed of sclerotic, yellowish white tissue. Occasionally one may see rarefaction of bone and even cyst formation grossly.

Other macroscopic changes have been noted but appear to be of lesser importance. These include: a generalized petechial or purpuric eruption of the skin and on the subserous or submucous tissues; small abscess-like areas of softening in the thymus, which resemble Dubois abscesses; early cirrhotic changes in the liver; rarely, grayish yellow, often excavated small nodules in the lungs, and, occasionally, localized masses either in viscera or over bones.

The essential unity of these widespread changes becomes apparent on consideration of the histology. Proliferation of large mononuclear cells occurs throughout the distribution of the system of histiocytes. In many places, particularly in the lymph nodes and to some extent in the marrow and spleen, this proliferation results in complete distortion of the normal structure. The cells are either irregularly rounded or of a bizarre polyhedral shape and may attain a tremendous size, measuring from 30 to 50 microns. They possess dense acidophilic cytoplasm with poorly defined boundaries, which are often altered by pseudopod-like extensions. The nuclei are round, oval or reniform and have a vesicular appearance; the nuclear membrane is distinct. Numerous multinucleated cells are seen, which bear a resemblance either to the Reed-Sternberg giant cell or to the megalokaryocyte with its annular convoluted nucleus. These cells are seen in discrete masses lying within endothelial-lined spaces and occupying the reticulum in the various locations mentioned before. By appropriate staining a marked proliferation of argyrophilic reticulum can be demonstrated in intimate contact with these atypical cells. Occasional mitotic figures are observed. The presence of intracellular and extracellular yellowish brown pigment has been noted in the spleen and other locations, usually near the periphery of an area of fibrous tissue proliferation. This was considered by Dameshek to be hemosiderin. Ritchie and Meyer noted clumps of eosinophilic crystals of unknown composition within widely distributed phagocytes. The effect of this widespread hyperplasia on the viscera can be best demonstrated, perhaps, by consideration of the following case:

REPORT OF CASE

A white man aged 51 years, a silverware salesman, was admitted to the service of Dr. Harry Stein on Dec. 18, 1936. He complained of severe pain in the lower region of the back and of generalized body aches of approximately two months' duration. The patient had been seen first at home on December 10, when these complaints were elicited. He had noted no chills or fever but complained of considerable sweating. Apparently, some degree of subjective relief was obtained at this time by the use of ordinary analgesics. However, on December 17 he again called his physician, and this time complained of having had several attacks of epistaxis. One of these had been severe enough to require packing by an otolaryngologist. At this time, also, a diffuse purpuric and petechial eruption, which was stated to have appeared only a few hours before, was noted. Immediate hospitalization was advised.

The family history is noncontributory. The past history reveals an attack of coronary thrombosis in February 1935. This was complicated about a month later by occlusion of the left popliteal artery, probably the result of the breaking-off of a mural endocardial thrombus. Amputation of the left leg below the knee was necessary at this time. In May 1935 he was readmittted for possible arterial obstruction in the right lower extremity. This, however, cleared up uneventfully. It is of interest to note that during these previous hospitalizations blood studies

revealed nothing unusual. In fact, a slight degree of polycythemia was noted during the last period in the hospital, when a red blood cell count revealed 5,780,000 cells per cubic millimeter and a hemoglobin content of 124 per cent, Sahli (18 Gm.).

Examination during the illness beginning in December 1936 revealed a well developed, somewhat obese middle aged white man, who was somewhat pale and rather dyspneic. Numerous purpuric and petechial lesions were noted scattered over the trunk, extremities, buccal mucosa, tongue and conjunctivae. All mucous membranes exhibited a distinct pallor. The axillary and the left inguinal lymph nodes were palpable. These nodes were discrete and not tender. They varied in size from approximately 0.5 to 2 cm. The heart was moderately enlarged to the left, and the blood pressure was 120 systolic and 80 diastolic. Only a few moist rales were heard at the bases of the lungs posteriorly. The margin of the right lobe of the liver could be felt extending approximately 3 fingerbreadths below the costal margin. The lower pole of the spleen could just be palpated at the costal margin on deep inspiration. On pressure over these organs there was moderate tenderness. Absence of the left lower extremity below the knee was noted.

No extensive laboratory studies could be carried out because of the patient's brief course in the hospital. However, the results of examination of the blood proved of interest. On admission the following picture was obtained: hemoglobin content, 59.4 per cent (Sahli 9.5 Gm.); red blood cell count, 3,380,000; color index, 0.89; white cell count, 9,250. The differential count revealed the following percentages: polymorphonuclear neutrophils, 23; polymorphonuclear eosinophils, 4; polymorphonuclear basophils, 2; myeloblasts, 2.8; neutrophil myelocytes, 1.8; eosinophil myelocytes, 1.3; lymphocytes, 28.4; monocytes, 24.8; monoblasts, 3.2. Three normoblasts were observed in the smear. The percentage of reticulocytes was increased to 1.1, and the number of platelets was reduced to 33,800 per cubic millimeter. A bleeding time of two minutes and a clotting time of five minutes were observed. The fragility test showed incipient hemolysis at 0.45 per cent and complete hemolysis at 0.30 per cent. The sedimentation rate was increased to 24 mm. in one hour.

Urinalysis showed an occasional hyaline cast and albumin (1 plus).

Studies of the blood serum were, of necessity, confined to the Kolmer and the Kahn test, both of which were negative.

The course in the hospital was of extremely short duration, approximately eighteen hours. At about 4 a. m., December 19, he suddenly became extremely dyspneic and the blood pressure dropped to 90 systolic and 60 diastolic. The respirations became increasingly labored, and death occurred at 5:50 a. m.

Autopsy.—Autopsy was performed three and a half hours after death. The report is abbreviated here, but no pertinent observations are omitted.

Externally, the only striking feature was a diffuse purpuric and petechial eruption over the trunk and extremities. Most of these lesions were of pinhead size, but in some locations, particularly on the chest, they were as large as 1 cm. in diameter. On section, the cavities of the body were found normal except for the presence of a few fibrous adhesions of the pleurae over the apexes of the lungs.

The heart was moderately hypertrophied, weighing 440 Gm. Scattered petechiae were observed in the subepicardial tissue. At the apex of the left ventricle were macroscopic areas of fibrosis and an old healed infarct. On the endocardium overlying the infarct, a partially organized thrombus was present. The coronary arteries were tortuous and displayed atherosclerotic changes.

The liver weighed 3,550 Gm. The surface was studded with irregularly rounded yellowish nodules, measuring from 5 mm. to 4 cm. in diameter (fig. 1). These were of a soft rubbery consistency and resembled metastatic nodules. On section, similar nodules were noted throughout all the lobes. Here, however, their homogeneous appearance was disturbed by spokelike narrow reddish brown striations. The intervening liver tissue was pale yellowish brown, with some accentuation of the normal lobulation. The gallbladder and the biliary passages displayed no macroscopic changes.

The spleen weighed 370 Gm. The surface was deformed by scars of several old infarcts which had healed and retracted. In addition, a relatively fresh infarct

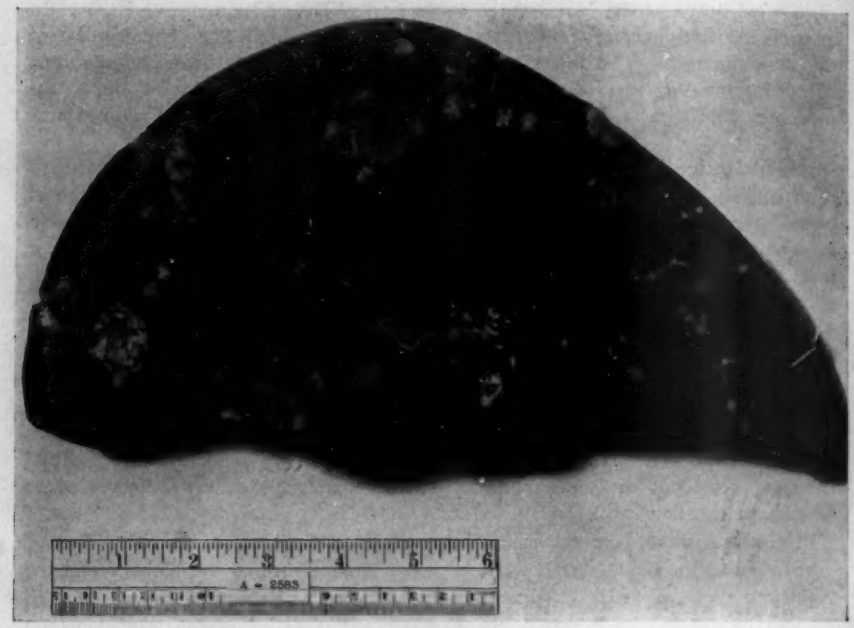

Fig. 1.—Cross section of the liver, showing discrete nodules of various sizes and accentuation of the normal intralobular markings.

was present. On section, a grayish red surface was observed. The normal markings were obscured, and poorly defined circular grayish areas were noted, merging into the dark red background.

The retroperitoneal, left inguinal and axillary lymph nodes were enlarged. The nodes were discrete and easily separable and measured from 1 to 4 cm. in length. They were soft and on section displayed a grayish brown striated surface.

Marrow from a rib and from a lumbar vertebra had a moist pinkish gray appearance.

The lungs displayed no remarkable gross changes except for an old healed fibroid tuberculous lesion in the right upper lobe. Moderate congestion and edema were noted.

The genitourinary tract displayed no gross changes with the exception of several healed infarcts in the kidneys.

The gastrointestinal tract was remarkable only for numerous submucosal purpuric lesions in the stomach. A tarry liquid material was found in the stomach, and the fecal contents of the intestines were of a similar color.

No gross pathologic changes could be detected in the pancreas or in the adrenals.

Permission for examination of the brain was not obtained.

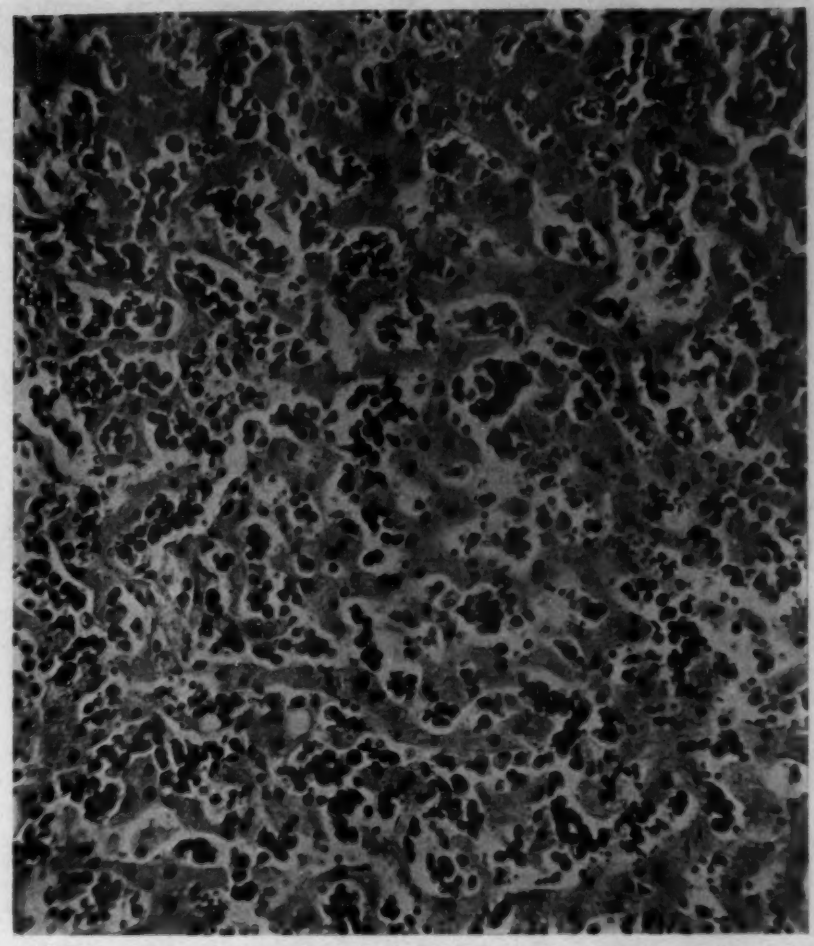

Fig. 2.—Liver; × 200. Note the large mononuclear and giant cells in the intralobular sinusoids. There is slight atrophy of the intervening cords of parenchymal cells.

A postmortem culture, made from blood of the heart, yielded a growth of Streptococcus anhaemolyticus.

Microscopic Examination.—The histologic observations proved of great interest. The more striking lesions will be described first.

In the liver there was distortion of the architecture by a process which involved practically all of the intralobular sinusoids (fig. 2). These were filled with large

(from 12 to 18 microns in diameter) mononuclear cells having abundant dense eosinophilic cytoplasm and hyperchromatic nuclei. The cytoplasmic borders were ill defined and often irregular. The larger cells often contained some phagocytosed granular débris. The nuclei were large and round or oval, with a distinct membrane and a reticulated chromatin network. An occasional one contained a distinct nucleolus. Fairly numerous multinucleated cells of the Reed-Sternberg

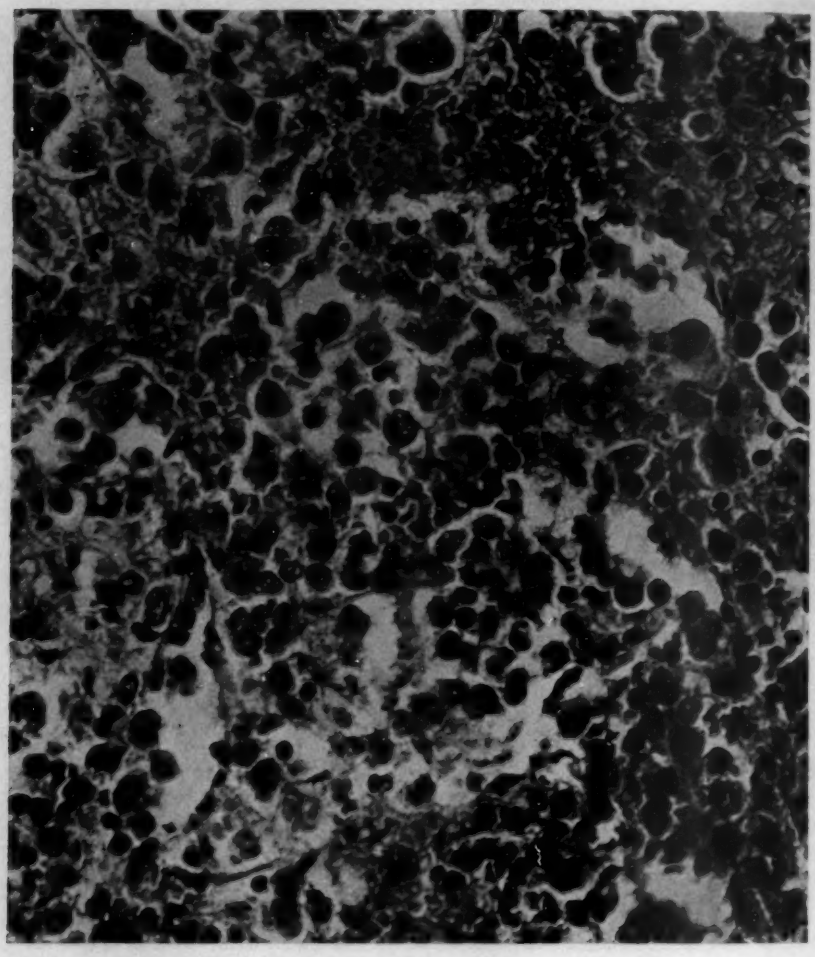

Fig. 3.—Spleen; × 520. Note the marked proliferation of reticuloendothelial elements in the pulp and the masses of cells lying within the sinuses.

type were seen. Most of these cells lay free within the sinusoids and had no particular stroma. Some cells were apparently attached to the lining of the sinusoids and resembled hypertrophied Kupffer cells. Pressure from these masses of cells had resulted in atrophy of the intervening cords of parenchymal cells, which were scarcely recognizable in some locations. The coalescence of masses of these cells gave rise to the macroscopic nodules which were described in a

preceding paragraph. Associated with the "type" cells described was an occasional mononuclear cell, its cytoplasm densely packed with large eosinophilic granules.

Marked hyperplasia of the reticuloendothelium of the splenic pulp had occurred (fig. 3). The malpighian bodies were atrophic. The cells seen in the pulp were

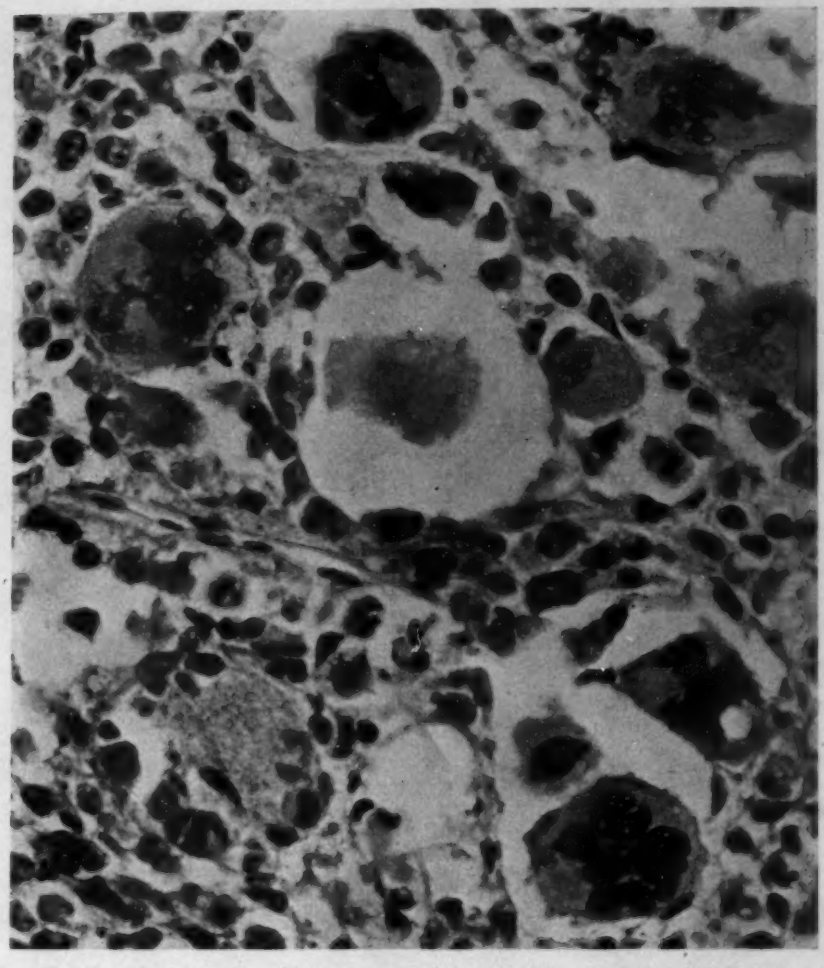

Fig. 4.—Lymph node. Note the complete distortion of the architecture and the replacement of lymphocytes by large mononuclear cells, also the bizarre giant cell forms.

similar in appearance to those already described. They were seen lying free within venous sinuses, in which the endothelium was somewhat edematous. The reticulum contained a predominance of these cells to the almost complete exclusion of the normal components.

The most striking picture, perhaps, was seen in the lymph nodes. The changes in a retroperitoneal node to be described here were characteristic of the glands wherever gross lymphadenopathy had occurred. Complete distortion of the architecture had taken place, and the node had a lobulated appearance as the result of marked proliferation of fibrous trabeculae. The entire node was occupied by type cells (fig. 4). There was, however, marked pleomorphism here, with a great

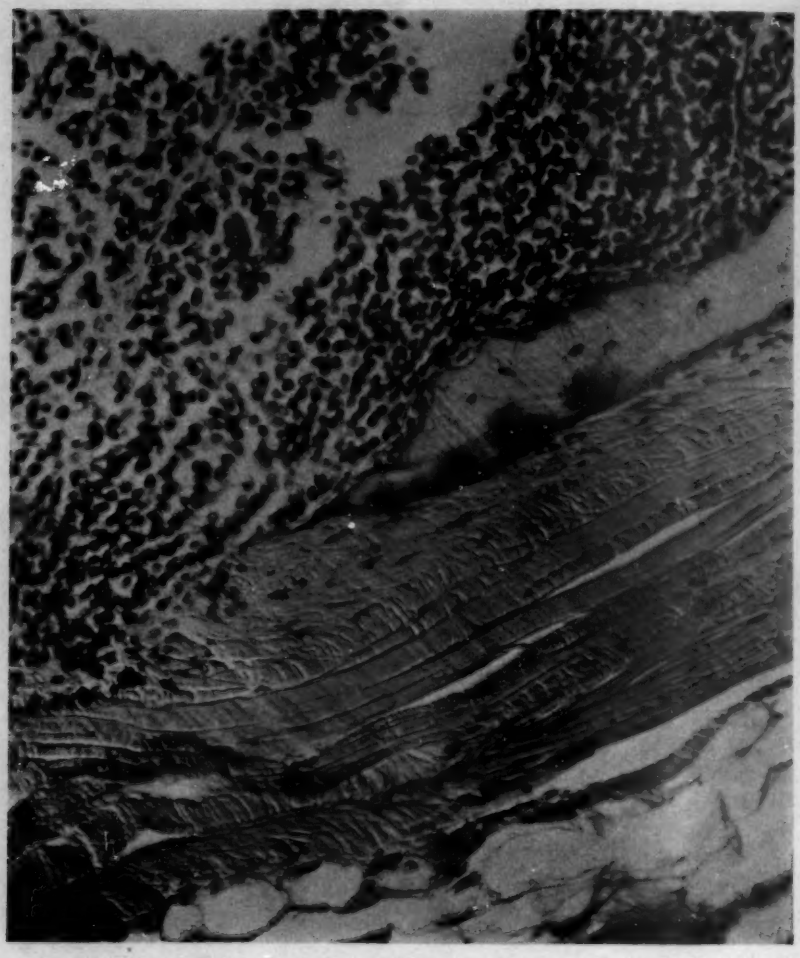

Fig. 5.—Rib; × 275. Note the proliferation of the reticuloendothelial cells, with erosion of the cortex and extension through the periosteum into the surrounding muscle.

many bizarre large uninucleated and multinucleated cells present. Some of the latter contained 10 or more nuclei, and in many instances these were arranged in a linklike fashion about the periphery, giving the cell the appearance of a megalokaryocyte. Numerous cytoplasmic and nuclear vacuoles were noted. In areas of fibrosis were masses of golden brown pigment, both within macrophages and free in the tissue. The capsule of the node was uninvolved.

Marrow from a lumbar vertebra and from a rib was examined. Marked hyperplasia was present, and the vast majority of the cells were of the mononuclear or of the giant cell variety described. Here, however, the cytoplasm of the cells appeared to form a syncytium. The cells could also be seen lying within vascular spaces. Only scattered foci of erythropoietic and myelopoietic tissue were present. In the rib the type cells had eroded through the cortex and were seen extending through the periosteum (fig. 5).

In the adrenals were noted several microscopic nodules, composed of type cells, which were confined to the capillaries of the cortex.

The aorta displayed slight proliferation of mononuclear cells about the vasa vasorum in the adventitia. In the intima atherosclerotic changes were noted.

On examination of the myocardium a small group of large mononuclear cells was seen apparently attached to the endocardium, and a similar small collection of free cells was noted within one of the veins of the myocardium. Ample evidence of myocardial fibrosis and an old infarct were present.

The remainder of the histologic observations are of only incidental interest. In sections of the lungs, an old healed tuberculous lesion was identified. Some alveolar walls were thickened by a slight increase in the number of large, rounded mononuclear cells. The kidney displayed several organizing infarcts, but the remainder of the genitourinary apparatus proved to be without lesions. The gastrointestinal tract, including the pancreas, displayed no changes.

All tissues were stained as a routine with hematoxylin and eosin. Among the special stains employed were Mallory's potassium ferrocyanide stain for iron, Foot's silver modification for reticulum and Herxheimer's scarlet red stain. No excess of lipoids could be detected in any of the involved tissues, nor did the abundant brown pigment in the lymph nodes give a reaction for iron. The stain for reticulum displayed an apparent increase in fine argyrophilic fibrils in most areas of pronounced cellular proliferation. These fibrils were in intimate contact with the type cells, but a direct association with the cytoplasm of these cells could not be demonstrated. The fibrils were noted surrounding individual cells and small groups of cells. The lobulation of lymph nodes was due to proliferation of the collagen.

COMMENT

With accurate description of an increasing number of cases, the entity reticuloendotheliosis is becoming more clearly defined both clinically and pathologically. It can readily be separated from the hyperplasias due to specific infections and those associated with disturbances of lipoid metabolism. With considerably less ease can one dissociate reticuloendotheliosis from the systemic proliferation of monocytic leukemia. Many would regard the aleukemic variety of the latter dyscrasia as identical with reticuloendotheliosis. There is no doubt a fundamental relationship between the two, but from the morphologic and the histologic point of view there are many differences. Their intimate interrelation, however, can be readily perceived in the light of recent experimental work. Furth [32] recently demonstrated the production in chickens of a great variety of reticuloendothelial reactions by means of a single filtrable agent of fowl leukosis. These reactions varied from ordinary hyperplasias to what he was satisfied to regard as tumors.

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In the recent study of a well defined case of monocytic leukemia and a consideration of cases reported in the literature, evident differences between these two forms of hyperplasia were noted. In reticuloendotheliosis one observes marked pleomorphism of cellular elements and atypical proliferation of reticulum. On the other hand, in monocytic

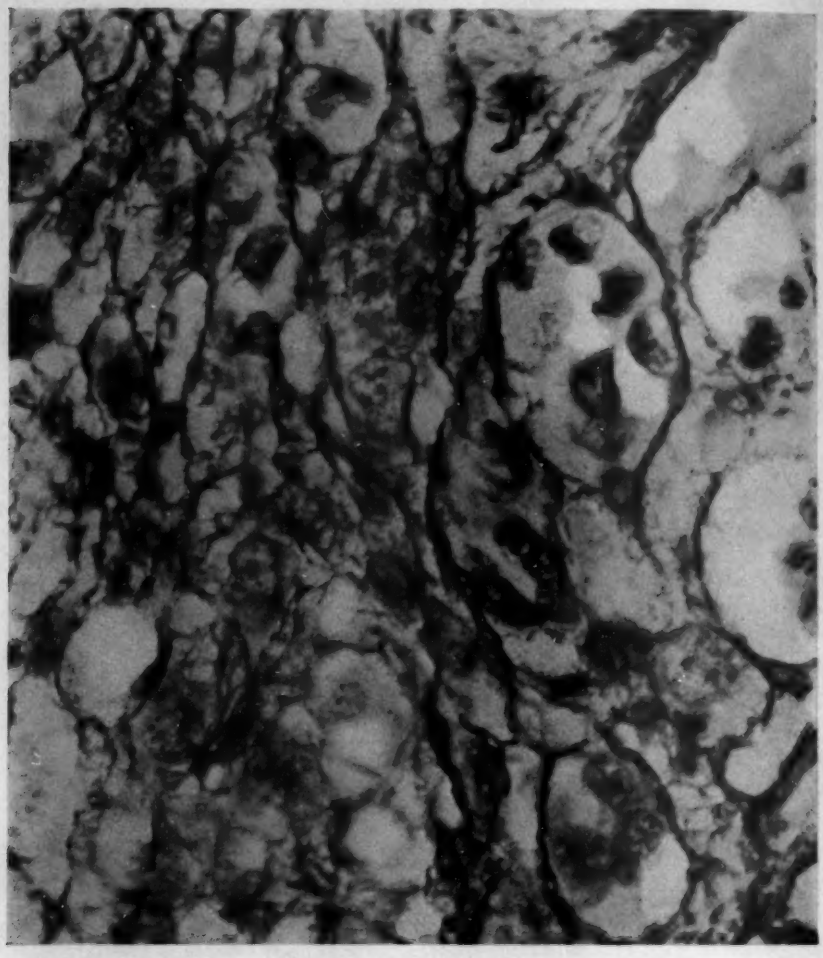

Fig. 6.—Retroperitoneal lymph node; × 1,080; Foot's reticulum stain. Note the atypical proliferation of the reticulum and the relationship to the type cells.

leukemia the cell type is more uniform and more widespread in the connective tissues of the body, and many times the process gives the appearance of infiltration rather than of hyperplasia in situ. The proliferation of reticulum observed in the leukemia appears to represent quantitative rather than qualitative deviation from normal. The invasion

and rarefaction of bone and formation of bone cysts are characteristic solely of reticuloendotheliosis. Nor is this entity distinctly analogous to leukosarcoma and chloroma. The blood picture in the latter two conditions is quite characteristic while in reticuloendotheliosis it is exceedingly variable. At the onset of this disease the hemocytologic pattern resembles that seen when there is stimulation of the marrow by metastatic malignant growth. To this there may occasionally be added distinct monocytosis, which is extremely helpful in arriving at a diagnosis. Terminally, the picture is frequently one of complete aplasia with reduction in the numbers of all formed elements.

The resemblance of this entity to Hodgkin's disease is striking and has been commented on by Dameshek, Wihman [33] and others. This resemblance has an adequate pathologic foundation, as the latter disease is being increasingly considered as a variety of reticuloendothelial hyperplasia. The two diseases possess many features in common, including moderate hyperpyrexia, generalized lymphadenopathy, splenomegaly, a tendency toward the formation of giant cells and toward the laying down of large amounts of reticulum. In reticuloendotheliosis, however, there is much more widespread systemic involvement than is apparent in Hodgkin's disease. The invariable involvement of the bone marrow, the extensive involvement of the liver and the marked pleomorphism of cellular elements also tend to distinguish the former from the latter. An absolutely sharp line of demarcation, however, has not been established between the two. In both one may occasionally observe transition into a definitely malignant process, retothelial sarcoma in one and the so-called Hodgkin's sarcoma in the other.

The problem of the ultimate nature of this process, whether neoplastic or inflammatory, remains as insoluble now as at the time of the excellent review by Foot and Olcott in 1934. Waugh [34] recently promulgated the idea of an intermediate variety of systemic hemopoietic proliferation, i. e., kataplasia, which would bridge the gap between hyperplasia and neoplasia. In this type of activity "the cells do not reach complete differentiation and often show atypical features of development, but they still exhibit evidence of environmental control and lack the apparent independence of true neoplasms." Both Hodgkin's disease and reticuloendotheliosis appear to fall into this convenient category. A toxic or a low grade bacterial stimulus has often been predicated in spite of the absence of proof. The etiologic status of this process remains thus suspended and must await clarification in further carefully studied cases.

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ATTRACTION OF HUMAN POLYMORPHONUCLEAR LEUKOCYTES BY TUBERCULOPROTEIN

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CLEVELAND

Many investigators have shown that human polymorphonuclear leukocytes are attracted by various micro-organisms. Thus it has been found in vitro that the tubercle bacillus exerts a positive chemotropic action [1] and that in experimental infections of animals [2] early infiltration of the infected areas by these cells occurs. The chemotactic response of leukocytes to bacterial fractions, however, has not been extensively investigated. Buchner [3] reported positive chemotaxis for the proteins of Friedländer's bacillus, Bacillus pyocyaneus and Bacillus typhosus, and Gabritschevsky [4] stated that bacterial filtrates attracted leukocytes. Dixon and McCutcheon [5] observed moderate attraction of leukocytes by the bacteria-free filtrate obtained from broth in which Bacillus coli had been grown.

In a long series of papers Sabin, Smithburn and Thomas presented studies of the cellular reactions of animals to various fractions of the tubercle bacillus. Smithburn and Sabin [6] found that "in the production of the specific lesions (of tuberculosis) the dead bacilli lack only the property of viability to place them on a level of importance with the living organisms." When injected into the peritoneal cavity of the rabbit the lipoid, protein and polysaccharide fractions severally induced reactions which could be easily differentiated. With the lipoid there was a profound cellular reaction, involving every type of connective tissue cell, as well as hemorrhage and the formation of tuberculous tissue and adhesions. [6] The proteins and polysaccharides, on the other hand, when injected intraperitoneally into rabbits, called forth a local response of leukocytes and phagocytes without proliferation of new connective tissue.[7] However, as these authors pointed out, the presence

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From the Institute of Pathology, Western Reserve University, and the University Hospitals.

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2. Lurie, M. B.: J. Exper. Med. **60**:163, 1934. Woodruff, C. E.: Am. J. Path. **10**:739, 1934.
3. Buchner, H.: Berl. klin. Wchnschr. **27**:673, 1890.
4. Gabritschevsky, G.: Ann. Inst. Pasteur **4**:346, 1890.
5. Dixon, H. M., and McCutcheon, M.: Am. J. Path. **12**:747, 1936.
6. Smithburn, K. C., and Sabin, F. R.: J. Exper. Med. **61**:771, 1935.
7. Doan, C. A.; Sabin, F. R., and Forkner, C. E.: J. Exper. Med. (supp. 3) **52**:73, 1930.

of leukocytes in the peritoneal exudate after the injection of a bacterial fraction does not indicate a specific reaction, because exudation of leukocytes follows intraperitoneal injection of any one of many foreign substances.

The attraction of leukocytes by nonspecific substances can be avoided by employing an in vitro method, and such a method has the added advantage of permitting the use of human polymorphonuclear leukocytes. For these reasons and because it seemed likely that the protein fraction of tuberculin might attract human leukocytes, the present experiments were performed.

METHOD IN FIRST SERIES OF EXPERIMENTS

A minute amount of the tubercle protein was placed on a clean glass slide and allowed to dry. In this way a small target from 50 to 150 microns in diameter was formed, and this was then covered with a thin, evenly spread film of human blood obtained from a finger prick. The preparation was sealed with lubricating grease and placed in a warm chamber at 37 C. The blood of three presumably healthy persons was used. After from fifteen to thirty minutes the preparation was observed under the microscope with a high dry objective (4 mm.), a small portion of the protein target being brought into the microscopic field. The course of each migrating leukocyte in the field was plotted on paper with the aid of a drawing ocular at intervals of one minute for a known period of time (thirty minutes). In this way it could be determined whether the leukocytes moved toward or away from the target or whether they moved merely at random. For each experiment a record was made of the behavior of the leukocytes at a distance (6 mm.) from the target. The outline of the protein target was drawn on another sheet of paper, and this outline was projected onto the microscopic field at a distance from the protein by means of the drawing ocular. This procedure had the same effect as placing an absolutely nonattractive substance in the microscopic field and was a perfect control experiment.[8]

The calculation of the degree of chemotropism (chemotactic index) was discussed at length by McCutcheon and Dixon.[1] In brief, the degree of chemotropism for any particular cell has been arbitrarily defined as the ratio between the net approach of the cell either toward or away from the target to the actual distance traveled by the cell. From this it follows that if the net approach of the cell and the actual distance traversed by it are the same the ratio will equal 1, which expresses the greatest possible chemotactic effect, either positive or negative. It also follows that the more nearly a cell approaches or leaves the target in a straight line the greater will be the degree of positive or negative chemotaxis, respectively.

The tuberculoprotein used was supplied by Dr. Florence Seibert, who prepared it from tuberculin by complete saturation of the latter with ammonium sulfate. It is referred to by her as "water-soluble tuberculin protein, b no. 50."[9]

8. McCutcheon, M.; Wartman, W. B., and Dixon, H. M.: Arch. Path. **17**: 607, 1934.

9. Seibert, F. B.: J. Biol. Chem. **78**:345, 1928. Seibert, F. B., and Munday, B.: Am. Rev. Tuberc. **23**:23, 1931.

RESULTS IN FIRST SERIES

In the first row of table 1 are the results of a series of experiments in which unadsorbed tuberculoprotein in the form of a dry powder was the source of attraction. In eight experiments 80 cells were observed and the mean chemotactic index was + 0.12, whereas in the control experiments the index of chemotropism was + 0.03. These values are so close to zero that they undoubtedly represent random motion. In other words, tuberculoprotein in its solid, undissolved form did not attract neutrophils.

TABLE 1.—*Summary of Experiments*

Substance Tested	In Field of Substance Tested		In Control Field	
	Cells	Mean Index of Chemotropism*	Cells	Mean Index of Chemotropism*
Unadsorbed tuberculoprotein	80	+0.12	71	+0.03
Tuberculoprotein adsorbed on kaolin	88	+0.57	66	+0.07
Tuberculoprotein adsorbed on charcoal	75	+0.09	87	+0.11
Kaolin	77	+0.05	94	—0.06
Charcoal	80	+0.28	85	—0.02

* The index of chemotropism is the ratio of the net approach of the cell toward or away from the target to the actual distance traversed by the cell.

Because it was thought that these results might be explained by the failure of the protein to dissolve in the blood plasma, another series of experiments was made in which tuberculoprotein was dissolved before being used as the chemotactic substance.

METHOD IN SECOND SERIES OF EXPERIMENTS

The protein powder was suspended in triply distilled water and sufficient tenth-normal sodium hydroxide was added to dissolve it; the solution was then neutralized (p_H 7) by the addition of tenth-normal hydrochloric acid. In this fashion a 1 per cent solution of the tuberculoprotein was prepared presumably in the form of the sodium salt.[10]

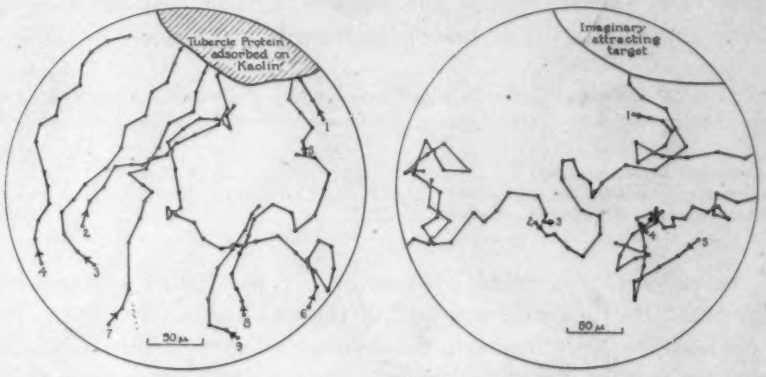
In order to see the protein solution under the microscope, it was necessary to adsorb the solution on some inert substance which could then be used as a target. Kaolin and charcoal, washed, were selected because they are easily available, are good adsorbing agents and are chemotactically inert. Equal amounts of the protein solution and a watery suspension of the adsorbing agent were mixed and allowed to stand at room temperature (approximately 23 C.) for thirty minutes. At frequent intervals the mixture was agitated. After adsorption of the protein the kaolin and charcoal particles were spun down in the centrifuge, and a small drop of the sediment was used as a target. In some experiments the particles were washed after adsorption, but this procedure did not alter the results. In control experiments kaolin or charcoal was used without protein.

10. Seibert, F. B.; Aronson, J. D.; Reichel, J.; Clark, L. T., and Long, E. R.: Am. Rev. Tuberc. **30**:707, 1934.

The record of a typical experiment and of the control is shown in the figure. In this particular experiment most of the cells moved toward the tuberculoprotein in a nearly straight line in contrast with those in the control area, which were obviously moving at random, so that only a single cell hit the imaginary target.

RESULTS IN SECOND SERIES

The second row in table 1 shows the results of ten experiments in which the tuberculoprotein was adsorbed on kaolin. Eighty-eight cells were observed and the mean degree of chemotropism was + 0.57 as compared with + 0.07 for the controls (66 cells). In one experiment, however, chemotaxis was negative, the mean value for the 5 cells observed being — 0.43. An explanation for this effect was not apparent,



Record of a typical experiment. The path of each leukocyte is represented by a line which connects a series of dots indicating the position of the leukocyte at intervals of approximately one minute. The record on the left shows attraction of the cells by adsorbed tuberculoprotein. The control record on the right shows another microscopic field at a distance from the tuberculoprotein. Here the cells are moving at random.

but the observation is thought to have resulted from some technical error, because all the other experiments had shown mean indexes of + 0.50 or more.

When unadsorbed pure kaolin was used as a target, the leukocytes moved at random, and low values of chemotropism (+ 0.05) were obtained, which were not significantly different from those obtained in the controls. Although these results appear clearcut and, as will be shown later, represent statistically significant differences, nevertheless it seemed advisable to eliminate the kaolin as a source of attraction by using some other inert substance. Charcoal obtained from sucrose (Kahlbaum) was chosen as the adsorbing agent because it had been found to be chemotactically inactive. The results of these experiments were similar to those obtained with kaolin. The mean value of chemo-

tropism for 75 leukocytes was + 0.69 when the tuberculoprotein was adsorbed on the charcoal and + 0.28 (80 cells) when unadsorbed pure charcoal was used.

COMMENT

Several points of technic must be explained. The question may be raised as to whether or not tuberculoprotein was adsorbed on the kaolin and charcoal. To answer this question, samples of the kaolin and charcoal with the adsorbed tuberculoprotein were analyzed for nitrogen by a micro-Kjeldahl method. An average of 2.34 mg. of nitrogen per gram of adsorbing agent (14.6 mg. of protein) was found on the particles after adsorption, whereas samples of the pure adsorbing agents contained no detectable nitrogen. Maschmann and Küster,[11] using kaolin, and Dorset, Henley and Moskey,[12] using charcoal, have also shown that adsorption of tuberculoprotein is impossible.

TABLE 2.—*Values of* X^2 *with the Corresponding Probability Equivalents (p)*

	X^2	p
Unadsorbed tuberculoprotein	11.82	0.115
Tuberculoprotein adsorbed on kaolin	669.90	0.000
Tuberculoprotein adsorbed on charcoal	21.25	0.005

In order to determine whether or not the results obtained were significant, the data were analyzed by the Chi square (X^2) test. Table 2 contains the X^2 values with the corresponding probability equivalents (p), for each of the experiments. Since a value of p above 0.05 is not regarded as significant, it follows that the weak attraction of the unabsorbed tuberculoprotein was probably due to chance. But with the adsorbed tuberculoprotein the chances that the results were due to random sampling are at the most only 5 in 1,000.

SUMMARY

In these experiments a study has been made of the chemotactic properties of one of the protein fractions of tuberculin (Seibert's "water-soluble tuberculin protein b no. 50").[13] In the undissolved state this fraction demonstrated no attraction for leukocytes. It was then brought into solution and adsorbed on kaolin or on charcoal. In this state it exhibited strong positive chemotropism in contrast with the weak chemotactic properties of the pure adsorbing agents. These

11. Maschmann, E., and Küster, E.: Ztschr. f. physiol. Chem. **193**:215, 1930.

12. Dorset, M.; Henley, R., and Moskey, H.: J. Am. Vet. M. A. **52**:373, 1926.

13. The chemotactic properties of the lipoid and of the carbohydrate fraction of tuberculin are being investigated.

results harmonize with those of McCutcheon and Dixon, who found that leukocytes were attracted by fractions of Streptococcus hemolyticus adsorbed on charcoal.[14]

CONCLUSION

Under certain experimental conditions in vitro, human polymorphonuclear leukocytes are strongly attracted by adsorbed tuberculoprotein obtained from tuberculin by complete saturation of the latter with ammonium sulfate.

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14. McCutcheon, M.; Dixon, H. M., and Czarnetsky, E. J.: Am. J. Path. **13**:645, 1937.

Historical Review

METCHNIKOFF'S CONTRIBUTION TO PATHOLOGY

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The early studies of Metchnikoff were concerned with zoology and zooembryology. The inception of his career as a pathologist dates back to the early 1880's (Metchnikoff was born in 1845) and was described by him in the following terms:

"I was resting from the shock of the events which provoked my resignation from the university and indulging enthusiastically in researches in the splendid setting of the straits of Messina.

"One day when the whole family had gone to a circus to see some extraordinary performing apes, I remained alone with my microscope, observing the life in the mobile cells of a transparent starfish larva, when a new thought suddenly flashed across my brain. It struck me that similar cells might serve in the defense of the organism against intruders. Feeling that there was in this something of surpassing interest, I felt so excited that I began striding up and down the room and even went to the seashore in order to collect my thoughts.

"I said to myself that, if my supposition was true, a splinter introduced into the body of a starfish larva, devoid of blood vessels and of a nervous system, should soon be surrounded by mobile cells as is to be observed in man who runs a splinter into his finger. This was no sooner said than done.

"There was a small garden to our dwelling, in which we had a few days previously organized a 'Christmas tree' for the children on a little tangerine tree; I fetched from it a few rose thorns and introduced them at once under the skin of some beautiful starfish larvae as transparent as water.

"I was too excited to sleep that night in the expectation of the result of my experiment, and very early the next morning I ascertained that it had fully succeeded.

". . . a zoologist until then, I suddenly became a pathologist."

Olga Metchnikoff, his wife, wrote apropos of his new orientation: "As long as Metchnikoff was but a zoologist the scientific atmosphere

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around him remained calm and serene. But everything changed suddenly when he entered the domain of pathology with the theory of phagocytes and phagocytosis."

What was the cause for this abrupt change of atmosphere?

The well known Malpighi and his contemporary Grew, were the first who demonstrated simultaneously in the seventeenth century, that the wood of plants is made of minute units (utriculi). That animal tissues, too, are constructed of microscopic units became apparent long afterward through the studies of Bichat, Carl F. Wolff, Robert Brown and others. However, cytology in the modern sense of the word was not inaugurated until the first half of the past century, when animal tissues could be studied with the aid of suitably constructed microscopes.

The histologic era began with the names of Schleiden and Schwann, who interpreted their observations according to botanical standards, and particularly with those of Henle, Remak, Reichert, Kölliker, Lebert and Charles Robin. Henle (1809-1885) is considered the founder of modern histology.

In 1859 appeared Virchow's *"Die Cellularpathologie."* According to Virchow, cells do not originate "out of moisture," out of simple cytoblastema [1] by means of direct precipitation of different substances, as originally postulated in the Schleiden-Schwann theory, but from preexisting cells. "Where a cell arises," wrote Virchow, "there a cell must have previously existed—*Omnis cellula e cellula.*" The cell, according to Virchow, is really the ultimate morphologic element in which there is any manifestation of life, and "we must not transfer the seat of real action to any point beyond the cell." [2] Not only is the cell the unit of life in health, but it is the seat of disease. Disease is "fomented" and propagated by the cell and not by bacteria as proposed by Pasteur. When Metchnikoff related his conception of the macrophage as playing a role in the defense of the organism against diseases, Virchow retorted that cells do not protect against, but, on the contrary, spread, a malady. The cell theory was accepted as a dogma. It was assumed by Virchow and his followers that each cell in the body is a separate center of activity, or that the body represents a republic of cells.

It was chiefly through the influence of Virchow (1821-1902) and Cohnheim (1839-1884) that morbid anatomy became one of the most

1. The cytoblastema, according to Schwann, is the intercellular substance which is destined for the development of new cells. According to this author, nuclei first form in fluid, and membranes (cytoplasm) do not form around them until later.

2. Remak, two years previously, had observed that cells originate from cells by direct division of the mother cell.

important disciplines in the medical curriculum. Their views dominated the teaching of pathology the world over for a generation.

It is well to review briefly some of the ideas held by pathologists in the 1880's, when Metchnikoff emerged with his conceptions of the mesenchyma and the mesenchymal reactions.

Pathologists of the past century, like their predecessors, looked at inflammation as a purely local phenomenon caused by irritation. "Irritation must, I believe," stated Virchow, "be taken as a starting point in the consideration of inflammation, and since Andral and Broussais regarded the matter in this light, I consider the views advanced by them to be the most correct." [3]

"Nowadays," he wrote, "we find the view is prevalent that in inflammation we have in the main to deal with a change in the act of nutrition, nutrition being here regarded as embracing the formative and nutritive processes. In consequence of some causes or other, external to the part which falls into a state of irritation, and acting on it either directly or through the medium of the blood, the composition and the constitution of the part undergo alteration. Simultaneously its relations to the neighboring parts are altered, enabling it to attract to itself and absorb from them a larger quantity of matter than usual and to transform it according to circumstances." As a result of "overfeeding" the cells are in a state of "cloudy swelling," which is responsible for the swelling or "tumor" so characteristic of inflammation. Virchow discriminated between parenchymatous and exudative inflammation; the latter—mucoid or fibrinous—is usually confined to mucous and serous membranes.

Cohnheim considered inflammation as primarily an alteration of the vascular wall which not infrequently is only "molecular" (*molekuläre Veränderung*). The other "mechanical" signs and symptoms that accompany inflammation, such as swelling and the passive outpouring of cells, are but effects resulting from the changes in the wall of the vessel.

To Virchow and to Cohnheim inflammation is the disease, which is essentially a harmful phenomenon.

In 1886 Stricker wrote as follows: "The modern conception of inflammation precludes the notion of 'hemitis' (inflammation of the

3. Broussais (1772-1838) was also the originator of the theory that irritation, viz., chronic inflammation, may ultimately induce cancer. Thus he stated: "All kinds of inflammations and subinflammations may produce cancer. In order to prevent scirrhous cancers of the uterine cervix, which occurs at the so-called critical period in women with painful menstruation, one must remove irritation of the uterus long before the advent of the critical period." Broussais similarly stressed the fact that cancer of the cardia, pylorus and other sites in the body may follow prolonged irritation.

circulating blood). Inflammation is primarily a local acceleration of the circulation and of the tissue changes, which in the soft parts consist in swelling. Such processes take place in tissues only and not in isolated cells. The notion of inflammation also embraces the tendency toward pus formation, that is, toward new cell formation."

It is noteworthy that the origin and nature of the pus cells were not understood by observers. Addison was not certain whether the pus corpuscles were merely extravasated colorless blood cells or whether the colorless white cells found within the vessels were pus corpuscles "which had been admitted to them from the exterior." Virchow emphasized that a pus corpuscle can be distinguished from a colorless blood cell by its mode of origin only.[4] "If you do not know whence it has come, you cannot say what it is; you may conceive the greatest doubt as to whether you are to regard a body of the kind as a pus or as a colorless blood corpuscle. In every case of the sort the points to be considered are, where the body belongs, and where its home is. If this proves to be external to the blood, you may safely conclude that it is pus; but if that is not the case, you have to do with blood cells." Virchow was less emphatic as to the origin of red cells, which, as he put it, "is still invested with a mysterious obscurity." However, in speaking of the then "fashionable" disease chlorosis, he remarks: "If we may conclude (as I certainly think one can at the present moment scarcely help doing) that the red corpuscles are brought to the blood from the spleen and the lymphatic glands, all this would indicate that in chlorosis a diminished formation takes place in the blood glands."

Virchow ignored the cellular components of the bone marrow. His failure to mention the formed elements of the bone marrow is noteworthy, because in 1849, ten years before the publication of "Die Cellularpathologie," Charles Robin pointed out that the red marrow contains large multinucleated cells, which he designated as myeloplaxes, and also a variety of small nucleated cells, which, to some appearances, were normoblasts. Neuman, in 1869, described anew the presence of small nucleated cells in the marrow and suggested a genetic relationship between these cells and the circulating erythrocytes. But even after Rindfleisch and Malassez, in 1880 and 1882, respectively, confirmed this observation, it was still disregarded or combated by their contemporaries. The opinion was widespread that the circulating red cells originate from "small white corpuscles" or else from giant cells which occur in some blood-forming organs. In the adult, it was stated, the red cells multiply by cell division. The multiplication of neutrophilic leukocytes was believed to occur in the circulating blood, where they

4. Virchow, in "Die Cellularpathologie," stated that cancer juice is distinguished from pus by the higher degree of development to which its individual elements have attained.

originate "from small cells furnished by different organs" (Bizzozero; Arnold). In 1887 Mosso, professor of physiology at the University of Turin, Italy, published an elaborate report, in which he adduced evidences that the granular leukocytes originate from red blood cells. The lobulated appearance of the polymorphonuclear leukocyte was interpreted by many authorities as a sign of degeneration (*degenerative Theilung oder Fragmentirung.* Löwit).

It was in 1879 that Paul Ehrlich devised the method of studying thin films of blood, dried and fixed by heat. The modern conception of the hematomyelolymphopoietic systems was advanced by him only toward the end of the century.

Of particular interest are the teachings on tuberculosis:

Following Laënnec, who identified the various anatomic forms of tuberculosis as representing different aspects of the same disease (unitarian conception), Virchow affirmed that "nearly everything that occurs in tuberculosis which has not the form of a nodule is inflammatory in nature and is not related to this disease. . . . In the lungs the tuberculous granulation tissue takes its origin in the peribronchial and perivascular tissues, while the pneumonias alleged to be tuberculous come from the alveolar epithelium and are confined to the interior of the alveolus itself. . . . Caseation has nothing that is especially tuberculous; caseous pneumonia does not resemble a tubercle. . . . Phthisis and tuberculosis are two different things" (dualistic conception). Virchow's views were universally accepted.

The experiments by Villemin revealed that tuberculosis is invariably induced in animals whether the inoculated material is made up of miliary tubercles, of granulation tissue or of extensively caseated tissue. As a result of these observations Laënnec's (unitarian) conception was revived and ultimately triumphed (Grancher, 1878). However, the anatomic and clinical aspects of tuberculosis were not understood. The opinion was prevalent that tuberculosis is a hereditary disease transmitted from mother to fetus by way of the blood stream. The tubercle was regarded as a "neoplasia," and the origin and nature of its components were oddly interpreted. Thus the cells of which the tuberculous tissue is made up were invariably traced to the "local fixed tissue." Giant cells were traced by Virchow to a proliferation of fat cells. Klebs found that they usually lie in the lumens of the lymphatics and may originate from "coagulated albuminous corpuscules." Pathologists of those days were impressed by the discovery of mitotic division of cells by Flemming, and whenever a cell was found in a state of karyokinesis, this was regarded as a specific response to the irritating microbe (*Karyokineisis der fixen Gewebszellen—das erste pathologisch-histologische Phänomenon . . . in Tuberculosis.* Baumgraten). Baum-

garten, in accord with the views dominant in the 1880's, traced the origin of the epithelioid cells in tuberculosis to "fixed tissue cells," which in the lungs consisted of the bronchial and alveolar epithelium, of the capillary endothelium and of the smooth muscle cells of the vessel wall (*die glatten Muskelzellen der Media betheiligen sich an der Erzeugung epithelioder Tuberkelzellen.* Baumgarten). In the liver, the progenitors of the epithelioid cells were the polygonal hepatic and the bile duct epithelial cells; in the kidneys, the tubular epithelium; in the iris, the lymph nodes, and in the spleen, the ubiquitous "fixed tissue cells," the nature of which was not explained.

Neoplastic diseases occupied a limited place in the laboratories of that epoch. While grossly tumors were usually identified, their histogenesis, mode of spread and histologic aspect were not understood. Cohnheim's well known theory of embryonic rests as being the source of all malignant tumors is still shared by modern observers for some categories of tumors. Virchow, in 1884, emphasized that "there are tumors, such as gliomas, which originate through hyperplasia of embryonic tissue. . . . I also reported observations [he relates] where elements of epithelial character originated from connective tissue by way of metaplasia. . . . I, for my part, am convinced that epithelial tumors may originate from connective tissue through metaplasia. . . . As far as pathologic-anatomic observations go, fat cells serve as matrices for epithelial cells, occurring partly through metaplasia and partly through proliferation." Virchow endorsed the interpretation of Gaucher's disease as originally given by Gaucher, in 1882, to the effect that it is a primary epithelioma of the spleen. This is of particular interest since Metchnikoff at this early stage had identified the large splenic cells as being of mesenchymal origin. Thus he wrote: "Foreign elements are devoured mostly by the large cells of the splenic pulp, which are true macrophages."

The conception was prevalent that the connective tissue is the matrix for all varieties of tumors. It was believed that in instances of proliferation this tissue readily reverses itself to an embryonic state and reproduces cells of different germinal layers (Virchow; Ranvier; Cornil).

A quotation from an article by Reynaud published at that epoch is significant. "In the present state of science," wrote the well known physician, "one no longer bases an anatomic diagnosis of cancer on the cellular morphology of which the tumor is made up, for it is never constant and may vary infinitely. Accordingly, one no longer admits the expression 'cancer cells' but 'cancerous tissue,' which consists, on one hand, of an alveolar fibrous stroma and, on the other hand, of cells lodged in the alveoli."

Indeed, while the pathologic literature of that period contained isolated contributions of great merit, pathologic anatomy generally was in a state of confusion.

Metchnikoff was the first to inaugurate and to stress the importance of comparative pathology. "Just as formerly in anatomy," he writes, "studies were limited to man and other highly organized animals, so at present in medicine one totally ignores the pathologic phenomena that affect the lowly organized creatures. However, the study of these animals which, unlike men and other vertebrates, yield simple and primitive processes, will furnish the key to the abnormal. Pathology," continues Metchnikoff, "is the only science which ignores comparative methods of study. As numerous inferior organisms—plants as well as animals—are susceptible to the formation of neoplasms, comparative studies of these beings would be helpful in the investigation of the problems of tumor formation."

Morbid processes occurring in man and lower animals were interpreted by Metchnikoff from a broad biologic standpoint. To him, the Darwinian, disease and defense against it have evolved through countless ages, having their inception in the primitive organism—the single cell. "If unicellular beings [as he repeatedly observed] possess means of defense, it is inadmissible that higher organisms are deprived of it. As a matter of fact, the higher organism has elaborated such means, as evidenced by the phenomenon of inflammation which, contrary to the general belief, is not a harmful but a defensive and salutary reaction of the organism." Inflammation is not just a local "painful" episode; it certainly is not the disease but is a response of the organism to the disease.

In the period preceding Pasteur the cause of many diseases was often attributed to miasmas or to chilling. With the advent of the bacteriologic era, these had been replaced by bacteria, and the notion was prevalent that the penetration of the micro-organism into the body was alone sufficient to inaugurate a disease. It was assumed, in the words of a contemporary, that *Bacillus plus Mensch, sei gleich Infektionskrankheit.*

Physicians, before the advent of Metchnikoff's teachings, gave little thought to the manner in which bacteria propagate within the organism; they were completely unaware of the relationship between the host and the invading micro-organism. Koch, Klebs, Waldeyer, Birch-Hirschfeld and others noticed bacteria within the cytoplasm of cells, but they dismissed this observation as trivial, unworthy of investigation. This phenomenon was designated as "invagination" of bacteria into the cells.

The ultimate disappearance of bacteria from the body was attributed to the rate of their elimination, which was thought to exceed that of

their proliferation. It was also stated that bacteria perish in the body under the influence of their own metabolic products, their detritus being eliminated with the different secreta and excreta. Baumgarten [5] wrote as follows: *Bacterien sterben im thierischen Körper von selbst ab* (Bacteria in the animal body die out by themselves). Flügge [6] stated: "Bacteria that have made their way into the blood stream are eliminated from the body by way of the kidneys and occasionally by way of other organs." In brief, the role played by the host in infection and resistance was not considered by investigators of that period.

Metchnikoff's teachings moved the host forward into the front of the picture. Unlike an artificial medium, the animal body is usually not a favorable soil for the proliferation of pathogenic micro-organisms. The animal body possesses an "organ" whose chief function is the defense against noxious substances of exogenous or endogenous origin. The "organ" is the middle embryonic layer, the mesenchyma and its cellular elements, which under suitable conditions meet the intruder and dispose of it by "ingestion and digestion." As the mesenchyma and its cells are ubiquitous and as their functions are identical throughout the body, they may be spoken of as a complex or a system—*der nahrungsaufnehmende Zellenkomplex;* also *le système phagocytaire.*

From a biologic standpoint the process of inflammation and that of its satellite, phagocytosis, which is essentially a function of the mesenchyma, should be considered as one of intracellular digestion. It is a vestige inherited by higher animals from their remote ancestors, the unicellular and lowly organized creatures.

"When we feed a sponge with very fine particles [relates Metchnikoff] we notice that they are engulfed and digested chiefly by ameboid cells which originate from the mesoderm. When a foreign element penetrates into the body of these animals, it is likewise caught and devoured by cells coming from the same source. Should the invaded particle be of such dimensions that a single cell is not strong enough to dispose of it, there accumulate numerous cells which wall it off. . . . When a lowly organized transparent *Auricularia* is fed with fine particles of protein or with grains of carmine or indigo, these are taken up by the cells of the middle germinal layer. . . . When a bacterial emulsion or the aforementioned dyes in solution are injected under the skin of the transparent *Bipinnaria* or the *Phillirrhoë,* one readily notices that the micro-organisms and the dyes, respectively, are instantly approached and devoured by the wandering mesodermal cells."

5. Baumgarten, P.: Lehrbuch der pathologischen Mykologie, Braunschweig, H. Bruhn, 1886, vol. 1, p. 114.

6. Flügge, C. G. F. W.: Fermente und Mikroparasiten, Leipzig, F. C. W. Vogel, 1883, p. 255.

The reactions of the higher and lower types of animals are identical, as can be deduced from observations on the fresh water crustaceans, the Daphniae, which are transparent and can be studied alive under the microscope uninterruptedly for several days. These animals are often infected by a parasitic fungus, the spores of which, introduced with the food, penetrate into the body cavity. They are particularly suitable for the study of pathologic processes, shedding light on questions of general medicine.

"When the Monospora penetrates into the body cavity of the Daphnia," writes Metchnikoff, "it is immediately approached by one or many blood corpuscles, who open a struggle with the invader. The blood cells adhere to the spore so firmly that only rarely are they separated from it by the force of the blood stream. In cases where many spores invade the body there occurs an accumulation of masses of cells, and the picture is an exact counterpart of that seen in true inflammation. . . . At times the individual white cells fuse together, forming plasmodiums (giant cells). . . . Besides the blood corpuscles, a similar role of phagocytosis is performed by *certain connective tissue cells* of the Daphniae which also devour living germs." (The italics are mine. B. M. F.)

The preceding statement is of interest because some writers have attributed to Metchnikoff the view that the cells found in the zone of inflammation are of hematogenous origin only. Metchnikoff early called attention to the identity of the large mononuclear cells of the blood and those of the connective tissue. He noticed that endothelial cells of the hepatic capillaries detach themselves from the walls of these vessels and appear as ameboid phagocytic stellate cells. He identified the clasmatocytes found by Ranvier in the milky spots of the omentum with the ameboid connective tissue cells scattered throughout the body. He stressed the fact that the lymph nodes, the spleen and the bone marrow abound in large ameboid phagocytes. To these organs he attributed a "prophylactic" (defensive) role and accordingly studied the natural history of infectious diseases in splenectomized animals. He found among other things that dogs, normally refractory to anthrax, contract the disease if their spleens have been previously removed.

As inflammation in the Daphnia occurs in the absence of a close vascular system, he ventured to express the opinion that the phenomenon of inflammation may occur without the participation of the vascular apparatus (later he changed this view). Genealogically, he philosophizes, inflammation is of an origin more ancient than that of the blood vessels, and from this standpoint one must attach great importance to the white blood corpuscles of the vertebrates. As stated earlier, observers of that epoch were unaware of the genetic and morphologic

aspects of the white blood cells and also of their significance in health and disease. Metchnikoff stimulated interest in this part (lymphomyelopoietic) of the mesenchyma, which was so brilliantly detailed in later years by Paul Ehrlich, who shared the Nobel Prize for 1908 with Metchnikoff.

Metchnikoff himself soon established the role of the polymorphonuclear (granular) leukocytes in infection and resistance and designated them under the generic name of microphages. These cells, endowed with lobulated, fragmented nuclei, considered by others a sign of degeneration, were found by him to represent another variety of wandering phagocytic cells. He observed that while in a number of instances the macrophage is the cell par excellence for disposing of bacteria, in others this is the function of the microphage, while in still others both varieties participate in the destruction of the invader. For example, in gonorrhea, says Metchnikoff, both types of cells are found in the pus, but the gonococcus is phagocytosed exclusively by the microphages while the macrophages take up polymorphonuclear leukocytes and red cells. In tuberculosis the microphages reach the field of inflammation first and gorge themselves with tubercle bacilli but are rapidly supplanted by macrophages, which phagocytose Koch's bacilli and the microphages. They also form the epithelioid cells.

Faithful to his hypothesis that the lower and higher types of animals react to infection in like manner, he passes from the crustaceans to the vertebrates. "Koch," he writes, "observed that in septicemia of the mouse the white corpuscles contain bacteria, but he dismissed the observation as trivial. It appears to me that in this case it concerned phagocytosis of the parasites by the white cells. However, as the cells had taken up too many bacteria they ultimately succumbed, thus releasing the offender." . . . "It was noted," he continues, "that frogs resist infection with the anthrax bacillus, but the nature of the resistance has never been explained." Metchnikoff stated that in the case of septicemia of the mouse the germs took the upper hand over the phagocytes, causing the death of the animal; in the case of anthrax the reverse was true.

These observations were received by pathologists with the utmost skepticism, being considered fantastic and grotesque. Ziegler first attributed the phagocytic theory to the ignorance of Metchnikoff, inquiring with sarcasm: "Who examined the specimens for him?" Later he stated: "Insofar as pathology is concerned the theory of phagocytosis has not contributed anything that is new" (*soweit sie—die Theorie der Phagozyten—die Pathologie betrifft, hat sie keine neuen Beobachtungen gebracht*). Fraenkel remarked: "The theory of phagocytosis attributes

astonishing proclivities to the protoplasma of the leukocytes: sensations, thoughts and deeds—a kind of psychic perception." Sanderson in his Croonian Lectures said: "The phagocytic theory—a teleological theory; . . . A hypothetical endowment of phagocytes with consciousness." The opinion expressed by Metchnikoff concerning septicemia of the mouse and the probable nature of the immunity of frogs to the anthrax bacillus intensely antagonized Koch against him.

To objections and criticisms coming from every quarter Metchnikoff's reply was . . . counterexperiment. He relentlessly pursued his work, piling up evidence on evidence. Thus he inaugurated studies on the infection of frogs with Bacillus anthracis, which confirmed his early hypothesis, namely, that "the white cells of this animal do not represent a favorable medium for the Davaine-Pasteur bacillus, as affirmed by Koch, but they hamper its growth, kill and digest it. . . . In erysipelas the streptococci are taken up and destroyed by the microphages. . . . In relapsing fever living spirilla are engulfed and digested by polynuclear leukocytes." Metchnikoff made the interesting observation that during apyrexia in this disease the spirilla are found not in the macrophages of the liver or bone marrow but in the granular leukocytes, the microphages, of the spleen. He brought his sections to Koch for examination, trusting that seeing is believing. "The great savant (Koch)," relates Olga Metchnikoff, "received him very coldly. For a long time, while examining specimens of the spleen in relapsing fever, he refused to recognize in them an example of phagocytosis. Though he was at last obliged to bow to evidence, he yet remained unfavorable to the phagocytic theory, and all his assistants followed his example. Metchnikoff was much surprised and grieved by the hostility toward his ideas, notwithstanding they were based on well established facts." Pasteur and Lister early adhered to Metchnikoff's views. "I at once placed myself on your side," Pasteur told Metchnikoff, "for I have for many years been struck by the struggle between the divers micro-organisms which I have had occasion to observe. I believe you are on the right road." Lister wrote: "If ever there was a romantic chapter in pathology, it has surely been that of the story of phagocytosis." In 1891 Lister invited Metchnikoff to address the International Congress of Hygiene and Demography, of which he was the chief organizer. After the session at which Metchnikoff exposed the role of the phagocytes in defense of the organism against bacteria, pointing out the importance of their motion toward the focus of inflammation, Lister approached him and said: "I think that in these purposeful movements one must look for something superior to a simple chemical affinity." "In these words," says Metchnikoff, "were expressed

the attraction of Lister to the mysterious, and the mystic religious disposition toward which he was inclined as a member of the Society of Friends." [7]

Further studies revealed to Metchnikoff that the so-called lepra cells are none other than macrophages which act as phagocytes, destroying bacilli in the interior of their cytoplasm. These cells gather in bunches to form the characteristic lepra granuloma.

Baumgarten, whom I have quoted, had just published his experimental studies on tuberculosis. Like nearly all his contemporaries, this pathologist was opposed to the theory of phagocytosis. He denied Metchnikoff's contention that the leukocytes participate in the process of tuberculization and derided the notion of the ameboid phagocytic

Members of the Congress of Hygiene and Demography, Section of Bacteriology, in 1891. Left to right, seated: E. Roux; Sanderson; Joseph Lister; Arloing; Fedor; Hunter. Middle row: Lehmann; Büchner; Gruber; Hankin; Hueppe; Metchnikoff; Kitasato; Fraenkel; Ruffer; Sherrington. Top row: Bardach; Adami; Nocard; Cheynes; Cartwright Wood; Frankland; Cunningham.

macrophage. Metchnikoff spoke of him as of *der systematische Antagonist der Theorie der Phagocyten.* While Ziegler stated that the struc-

7. Metchnikoff met Lister on several occasions. He speaks of him in glowing terms: "His beautiful, expressive face with gray whiskers denoted an amiable disposition. His personality inspired high idealism. Beneath his somewhat cool appearance was hidden a warm heart. His behavior was simple, and his speech was fluent. In all his behavior and in the manner of his life, one felt a profound nobility. . . . Judging from what is known of Charles Darwin, Lister resembled him in many respects. There was nothing mean or egotistical in him. He was a gentleman in the best sense of the word." (Metchnikoff, 1915.)

ture of the tubercle varies with each individual, Baumgarten found that its components vary with each organ. His theory of the "fixed tissue cells" was detailed earlier in this paper.

Metchnikoff was the first who isolated the mesenchyma as an "organ" of defense and metabolism. He accurately described the morphologic aspect of the mesenchymal reactions. He likewise was the first to describe the structure of the miliary tubercle in tuberculosis. He laid the foundation for the discrimination between a granuloma and a blastoma (neoplasia), which hitherto was not clearly understood.

"The tubercle throughout the body," wrote Metchnikoff, "is made up of a collection of phagocytes of mesodermic origin, which flock toward the areas where the bacilli are located and engulf them." He thus stressed the morphologic and the physiologic aspects of the process, namely, that in inflammation the cells do not accumulate as a result of a passive transudation, as claimed by Cohnheim, but actively migrate (flock) toward the affected area. . . . "If we examine the liver we find that the tuberculous cells—the epithelioid as well as the giant—are formed exclusively at the expense of the phagocytic elements, that is to say of the large mononuclear leukocytes and of the Kupffer stellate cells, which are of endothelial origin. In no instance is the tubercle formed by a hepatic or by any other epithelial cell. It is true that the polygonal liver cells occasionally show mitotic division, but this is not related to the formation of the tubercle; it merely shows regeneration of the hepatic polygonal cells. . . . In the spleen and the lymph nodes the tubercle results from the agglomeration of large mononuclear phagocytes of these organs while in the lungs the tubercle is formed from the cells of the vascular endothelium with the assistance of the leukocytes. Giant cells, too, taking part in the formation of the tubercle, are none other than epithelioid macrophages which have united together in order to digest clumps of bacteria. After a while lymphocytes also gather from the circulating blood, assist in building the tubercle and ultimately transform themselves into large ameboid phagocytes." [8]

At this juncture Metchnikoff renounced his original view that blood vessels do not necessarily participate in the field of inflammation in

8. Metchnikoff's description of the mesenchymal reactions and of the formation of the tubercle is clear and unequivocal. Nevertheless he was misquoted by many investigators. This is particularly true in the case of the late Alexander Maximow, who in his study on tuberculosis of mammalian tissue in vitro wrote: "Metchnikoff and others claimed for the epithelioid cells an origin exclusively from the blood leukocytes." This, of course, is not in accord with the facts. Concerning the role of the lymphocytes in inflammation, Maximow wrote in the same article: "In 1902 I showed that the migrated lymphocytes in the field of inflammation transform themselves into ameboid phagocytic cells, the polyblasts." Although the transformation of small lymphocytes into macrophages in vivo is still debatable (Hall and Furth), nevertheless it was Metchnikoff who first described it.

vertebrate animals. "After the leukocytes," he wrote, "the vessels and the endothelium play the most important role in inflammation." His belief in the phagocytic properties of the endothelium was based on his earlier studies of the lowly organized animals provided with only two germinal layers—the endoderm and the ectoderm, the former playing the role of "digestion (metabolism) and defense." The concentration of these properties in the mesenchyma, which originates from the endoderm, begins, according to Metchnikoff, with the sponges.[9]

In the early part of this paper it was stated that since the time of Virchow, the notion has been prevalent that the connective tissue is the matrix of all varieties of tumor; also, that the "fixed tissue cells" are the source of the cells found in the area of inflammation. As regards neoplastic diseases, this view was contradicted by Brault, Menetrier, Waldeyer and others, who affirmed that only sarcomas originate from connective tissue, while cancer originates from epithelial cells. Bard is credited with the statement: *Omnis cellula e cellula ejusdem naturae.* The type and also the source of cells that occur in inflammation remained a stumbling block to pathologists who failed to understand Metchnikoff's ideas. Some observers have modified their views from those of "fixed tissue cells" to those of "fixed connective tissue cells" without, however, producing evidences in support of their new orientation; also, without understanding the manner whereby the new cells are formed. The majority of pathologists finally adopted the view that the vascular endothelium is the cell par excellence which displays potentialities in inflammation. Cornil begged the question thus: "The endothelium, which is so widespread in the organism, since it lines the splanchnic, articular, synovial and tendinous surfaces and also the blood and lymph vessels, plays the most essential role in the process of inflammation." It was then assumed that the ameboid phagocytic macrophages are always derived from the endothelial cells of the blood vessels and accordingly they were designated as the endothelial leukocytes.

Extensive studies on man and lower animals and in tissue cultures have disproved this view. Convincing evidences have been produced to show that, as Metchnikoff had it, the cells in the zone of inflammation

9. "The simplest Metazoa, such as sponges, are built of organs originating from the usual three germinal layers. The embryos of the sponges and the medusae reveal two layer stages, the outer enveloping the larva, the inner forming either a solid mass (parenchyma) of amebcid cells, or a layer of epithelial cells which line a digestive cavity. From the genealogical standpoint, the first type is the more primitive. It is named Phagocytella, because some of its cells ingest solid particles and, particularly, because of the fact that this layer yields the digestive cells of the fully developed organism. It produces the endoderm, which lines the intestinal tract with its appendages, and the mesoderm, which contains a multitude of digestive cells or phagocytes" (Metchnikoff).

originate in loco from the cells of the loose connective tissue and also from the white cells of the circulating blood. It was years before Metchnikoff's "Cellular Pathology" was accepted. The work conducted by pathologists and histologists for the last three decades has served to bear out Metchnikoff's conception of the mesenchyma and of the mesenchymal reactions. The idea that inflammation is essentially a salutary process is no longer contested. Metchnikoff's teachings opened a new world to investigators. Danchakoff, in recent studies in connection with resistance against heteroplastic grafting and also in connection with resistance to some transplantable tumors, has reached the conclusion that: "The adult splenic mesenchyma of the fowl has the power of encapsulating living Ehrlich sarcoma cells in the allantois of the chick and of submitting such tumor cells in the intracytoplasmic cavities so formed to a process of gradual digestion. . . . The phagocyte in this case is not a single cell but a mesenchymal syncytium with a common cytoplasm and numerous nuclei; the object of attack is the living cell of a mammalian tumor."

The view that the mesenchyma represents a syncytium of cells whose chief function is that of defense and metabolism was expressed by Metchnikoff for the first time in 1883, when he designated it as *nahrungsaufnehmende Zellenkomplex* (mentioned earlier in this paper), also as *le système phagocytaire*. He inaugurated the method of vital staining in order to trace the distribution of this cellular network. With this purpose in mind he investigated the fate of the easily identifiable nucleated red cells of the goose injected into the system of the laboratory animal. His young assistant, Besredka, studied, in 1899, the action of arsenic trisulfide on animals that had been previously treated with carmine. Besredka noted that under the conditions of his experiments guinea pigs tolerated intraperitoneal injections of arsenic trisulfide, the toxic substance being rapidly phagocytosed by the macrophages. But those animals which had previously received injections of carmine succumbed to the subsequent treatment with arsenic. The large mononuclear phagocytes "gorged" with the dye remained indifferent to the arsenic, which caused the death of the animals. Another of his assistants, Bardach, in 1899, found that dogs naturally immune to anthrax succumbed to the disease when a suspension of charcoal in water was previously injected into their blood. The preliminary injection of charcoal was done in order to "deviate phagocytosis" or, as he put it, *dans le but de détourner la phagocytose*. As in Besredka's experiments, the large phagocytes, satiated with the charcoal, remained passive toward the *bâtonnets* (little rods), which ultimately caused the death of the animals. This type of experiment has been designated by subsequent investigators as a blockade of the reticuloendothelial system.

Metchnikoff thus defined distinctly the conception of the so-called reticuloendothelial system, which he designated as *le système phagocytaire* (I use the term "macrophage system"). It served to him and to hosts of investigators for decades to come as a point of departure for the study of the most noteworthy problems in biology and medicine.

CONCLUDING NOTE

I have briefly reviewed the work of Metchnikoff, pertaining chiefly to the mesenchyma and to its reactions, to inflammation and to the theory of phagocytosis, against the background of ideas held by his contemporaries and predecessors. His ideas were new and heterodox. At first vigorously opposed and derided, they are now accepted, and every student of pathology and medicine has become in a sense a beneficiary and direct legatee of Metchnikoff. His teachings opened a new world to investigators.

Emile Roux, director of the Pasteur Institute, wrote about Metchnikoff as follows: ". . . You have kindled in the Pasteur Institute a scientific beacon which radiates far and wide. Your laboratory is the most animated corner in the 'House.' "

With the advent of the World War the activities of the "House" had virtually ceased, and the beaming light was obscured. Metchnikoff, deprived of his assistants, who had departed for the battle front, remained alone. In his solitude he conceived the idea of telling the world the life story of three scientists whom he knew so well. These scientists—Pasteur, Lister and Koch—were proclaimed by him as Founders of Modern Medicine.

To these great names another may be added—Metchnikoff.

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Case Reports

PRIMARY RHABDOMYOMA OF THE HEART WITH SARCOMATOUS EXTENSIONS

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In reviewing the literature on rhabdomyoma and sarcoma of cardiac origin one is impressed by the extreme rarity and the cellular diversity of such growths and the total absence of any specific diagnosic syndrome. Since 1835, when Albers reported the first authentic primary tumor of the heart, down to the present, there have been approximately 155 primary cardiac tumors recorded, 45 of which were classified as sarcomatous.

Ewing [1] described rhabdomyoma in general as being rare and of wide distribution in the body; in the largest proportion of the cases it was found in the genitourinary system. Most of the cases have been discovered in young persons; in some the growth was congenital. The gross forms have been single, multiple, nodular, flat or rounded, circumscribed or diffuse, or polypoid. On the cut surface they are usually soft and gray; the more cellular forms are red. Microscopically, parallel bundles or intertwining bands of striped muscle fibers have been described. These fibers are diffuse, seldom adult, usually thin and elongated and rarely branching. Longitudinal and cross striations may be present in the tumor cells or absent. The embryonal, or spindle-shaped, forms may retain only longitudinal fibrillations. The cells may resemble smooth muscle cells. Ribbert described large vacuolated cells with concentric striation of the perinuclear cytoplasm. In younger types the cells are spindle shaped, shorter and even round, losing all resemblance to muscle elements. Such variation, however, is seldom universal, foci of cells definitely myogenic in character being retained. Metastatic portions may consist of cells showing no muscular features. The nuclei of rhabdomyoma are large vesicular chromatic bodies; they are single or multiple, lying in a central area of granular cytoplasm. In certain parts of these tumors it is difficult to determine whether the cells are voluntary muscle fibers that have lost their striations or cells of the smooth variety. It must be remembered that undifferentiated cells may closely resemble smooth muscle. Some observers have claimed that metaplasia of smooth muscle elements to striated forms occurs, but embryology derives the voluntary variety from mesothelial plates and unstriated forms from the mesenchyme.

In a study of congenital rhabdomyoma of the heart Wolbach [2] reported 12 cases, in which Ponfick found the growth in the heart to be associated with diffuse sclerosis of the cerebral cortex and somatic nutritive disturbances. The theory is advanced that this type arises

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1. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1934, pp. 234-239.

2. Cited by Goldstein.[3]

from embryogenic disturbances in the structure of the heart. Bonome [2] traced the rhabdomyoma to fetal malnutrition, causing cerebral atrophy and sclerosis, and to a fibrous overgrowth in the heart, leading to separation of embryonal cells and nests, from which the tumors develop.

Goldstein [3] stated that sarcoma of the heart occurs at all ages but most commonly in the vigorous years of life. Various histologic types have been observed, the spindle cell variety being the most prevalent. An auricle is more often the site of the tumor than a ventricle. Rather common associated findings have been pericardial and pleural effusions with general edema. Goldstein reported a primary sarcoma of the heart with metastases to the lungs and pancreas, and 7 cases of metastatic sarcoma of the heart.

Perlstein [2] maintained that "of the various organs of the body the heart is the least frequent site of primary neoplastic change." Adami [2] stated that "the heart above all organs is constantly in a state of great efficiency, well nourished, well innervated, and functionally always active so that it is less likely to take on aberrant growth."

While historical records credit Boneti (1700) and Morgagni (1762) with reporting cardiac tumors, it is thought that the first authentic cardiac sarcoma was reported in 1865 by Bodenheimer.[2] Dating from this period, several sarcomas have been described, ranging from round cell to spindle cell type, the growth in the great majority of cases hanging within the auricle and being without metastases. Meroz found 3 primary tumors in 3,000 autopsies. Two were possibly organized thrombi, and the third was a spindle cell sarcoma, hanging down into the left ventricle through the enlarged mitral valve. There were no metastases in this case.

Link,[2] in his review of 91 cases of primary cardiac tumor, found that the growth was in the left auricle in 24, in the right auricle in 10, in the right ventricle in 14 and in the left ventricle in 8. In 16 cases it was a valvular tumor, and in 2 it was in the auricular septum. Perlstein [2] classified the collected instances of cardiac sarcoma histologically as follows: spindle cells, 10; round cell, 6; giant cell, 4; myxosarcoma, 3; fibrosarcoma, 3; mixed cell, 3; angiosarcoma, 1, and lymphsarcoma, 1. A total of 31 cases were studied, comprising 16 in males and 10 in females. Two of the patients were 3 and 7 years old. Three were 72, 76 and 79 years old. Meroz, who credited Virchow with the first description of a primary cardiac myoma, collected 55 instances from the literature. The site of predilection for 75 per cent of these was the left auricle. Stengel and Fox [2] pointed out that "organized, pedunculated thrombi have frequently been mistaken for tumors."

Reeves and Michael [4] presented the case of a 16 year old girl who complained of shortness of breath and rapid pulse. She died almost immediately, with a preautopsy diagnosis of bronchopneumonia with cardiac failure. The autopsy revealed both auricles replaced by a soft, friable nodular growth, which was markedly hemorrhagic. The heart weighed 880 Gm. Histologic examination disclosed cells of an embryonic type, among which small, fat spindle cells predominated. These were hyperchromatic and contained mitotic figures. Giant cells were fairly

3. Goldstein, H. I.: New York State J. Med. **115**:97 and 158, 1922.

4. Reeves, J. M., and Michael, P.: Am. Heart J. **11**:233, 1936.

numerous, and invasion of the ventricular wall was noted. They considered the growth to be primary rhabdomyoma of the heart. Ten cases of the skeletal variety have been reported since 1913. Much difficulty has been encountered in recognizing tumors of this type. MacCallum [5] stated, "Since the criterion demanded before an origin from muscular tissue will be admitted is the demonstration of the characteristic cross striations, it is not at all improbable—indeed it is almost certain—that many tumors truly of such origin or character are not recognized as such, and are relegated to the tumor scrap heap of sarcoma."

REPORT OF A CASE

A woman aged 37 was admitted to the Western Washington State Mental Hospital April 8, 1936, with a diagnosis of dementia paralytica. The salient points of the past history were: one full term, normal pregnancy, in 1921, an appendectomy and known syphilitic infection. She was well nourished. There was a slight systolic murmur over the apex of the heart. The neurologic findings were characteristic of syphilitic meningoencephalitis, and the serologic reactions were typical. Malarial therapy was started in August, 1936, which consisted of eleven chills. She stood the treatment well. March 9, 1937, she presented symptoms of pneumonia and died four days later.

Autopsy.—An examination made twenty-four hours after death showed pneumonia of both lobes of the left lung, right hydrothorax, a scar in the apex of the left lung, caseation in the hilar and mediastinal lymph glands and atelectasis of the right lung. An interesting incidental observation was a heavy calvarium, averaging 1 cm. in thickness, the increase being due to bony proliferation.

On the lateral wall of the left auricle there was a polypoid tumor, which hung down through the mitral valve into the left ventricle. The tumor measured 7 cm. in length and 6 cm. in width and was attached by a wide stalk to the wall of the left auricle. It was pale reddish gray and covered with endocardium, had a rather smooth surface and firm consistency and was semilobulated. It was composed of a homogeneous reddish gray tissue. The right pulmonary veins were filled with soft, friable reddish gray tissue. Similar growths invaded portions of the lung near the hilus. A small, isolated rhabdomyoma was found in an adjacent portion of the left auricular wall.

Microscopic Examination.—The main tumor mass showed marked histologic differences from the basal portion and pulmonary extensions (fig. 1). It was composed of interlacing bundles of closely packed spindle-shaped cells of a relatively benign character. The myogenic origin of the tumor cells was clearly demonstrated by the presence of numerous fibers in which were seen both longitudinal and cross striations. A few cells greatly resembled cardiac muscle fibers of an embryonic type in that they were large and ribbon shaped and contained centrally placed nuclei. Occasional large, multinucleated, hyperchromatic giant cells were present. The atypical large spindle cells, which predominated, contained elongated nuclei. About half of these nuclei were densely hyperchromatic, the remaining ones being vesiculated. The cytoplasm of the spindle cells was granular and eosinophilic and contained longitudinal striations. Close scrutiny of the giant cells disclosed multiple nuclei lying within dense granular cytoplasm. There was a suggestion of perinuclear concentric striations. A fine fibrillary connective tissue stroma was present. The tumor was well vascularized by sinuses, some of which

5. MacCallum, P.: Australian & New Zealand J. Surg. **2**:296, 1933.

Fig. 1.—Body of the main tumor mass, showing cross striations in myomatous cells. A giant spider cell is present.

were lined by low endothelial cells while others seemed to be mere channels through the tumor tissue which were filled with blood. Small areas of necrosis were present. There were foci of polymorphonuclear exudation and hemorrhage.

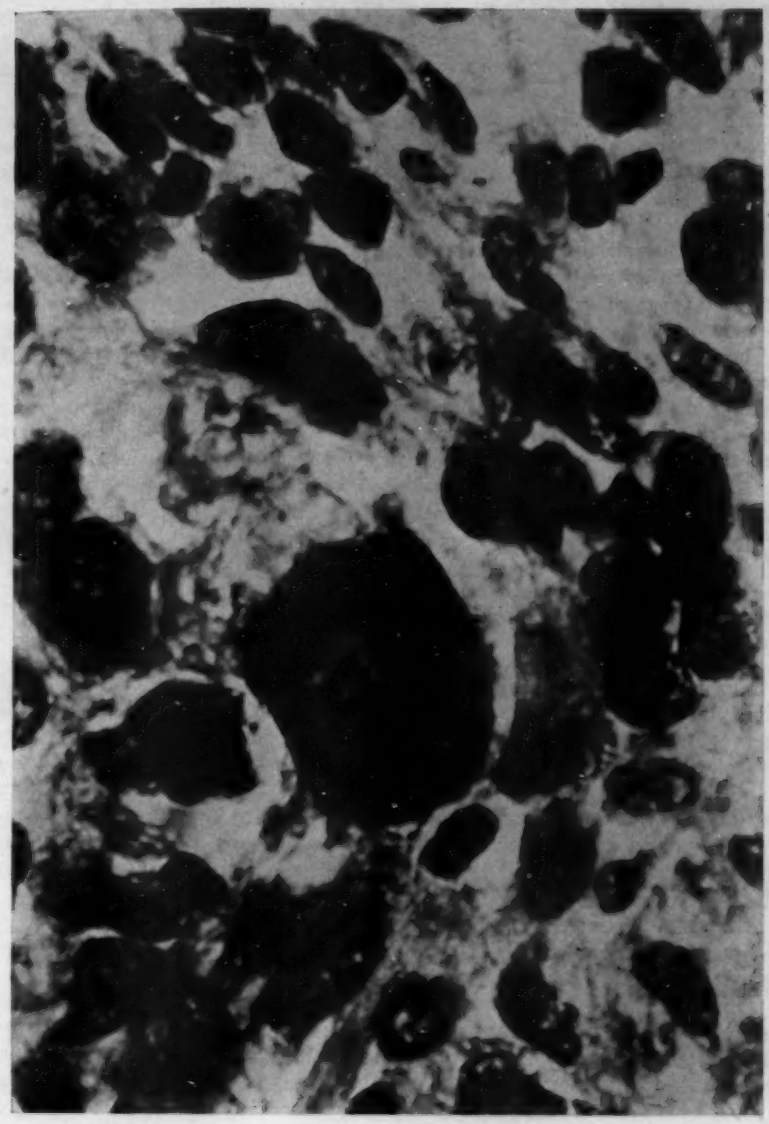

Fig. 2.—Stalk of tumor, showing sarcomatous characteristics.

The base of the tumor and the pulmonary extensions (fig. 2) were composed of closely packed cells of irregular sizes and shapes. These cells had large hyperchromatic nuclei, large nucleoli and scanty cytoplasm, in which no cross striations

were present. The stroma of this area was less dense than that of the body of the tumor; endothelial-lined blood spaces were not found, and foci of necrosis were more frequent. Many cells contained mitotic figures. The general appearance of this portion of the tumor indicated the presence of a much more atypical, embryonic and malignant neoplasm than did the main tumor mass. Entering the stalk of the tumor was a large nerve trunk, and nerve fibers were observed throughout all portions of the tumor, many of which could be traced directly to endings in the nuclei of tumor cells.

The right pulmonary veins were filled and completely occluded by tumor tissue, which resembled the sarcomatous elements found in the stalk of the tumor. The smaller branches of the pulmonary veins within the right lung were filled with a similar tissue. There were extensions of an infiltrative and destructive character into the pulmonary parenchyma. The surrounding lung tissue was in a state of pneumonic consolidation.

Within the kidneys were found small nodules, 1 mm. in diameter, which microscopically appeared to be composed of cells that resembled those of the main cardiac tumor.

The brain weighed 1,008 Gm. There was a moderate amount of subarachnoid edema. The vessels at the base were well preserved and of normal distribution. Intense pial hyperemia was present. The cut surface of the brain after fixation in solution of formaldehyde U.S.P. revealed atrophy of the cortical and nuclear gray matter, with dilation of the lateral ventricles. Microscopically, there were foci of round cell exudate about the parenchymal and meningeal arteries, with some thickening and edema of the leptomeninges. Cortical atrophy and glial sclerosis were present. All of these changes may well have been caused by the syphilitic meningoencephalitis, but, on the other hand, cortical atrophy and glial sclerosis often accompany primary rhabdomyoma of the heart.

COMMENT

From a careful study of Ewing's and Ribbert's "spider cells," (giant cells having perinuclear concentric striations) and from close observation of the related giant cell types seen in the primary tumor mass in this case (fig. 1), there appears a possibility that such a cytoplasmic structure may be due entirely to cross section of large ribbon-like, definitely embryonal cardiac cells. A similar analogy may be pointed out in dealing with longitudinal sections of mature smooth muscle fibers, as compared with cross sections of the same, showing the well known and easily recognized Cohnheim's fields.

The case reported is particularly unusual inasmuch as a review of the literature failed to disclose a single case of primary rhabdomyoma (benign) in which malignant change to rhabdomyosarcoma occurred.

This malignant change was present in the stalk of the tumor and was also seen in the extensions into the pulmonary veins and lungs. The demonstration of the large nerve trunk entering the stalk of the tumor and of the nerve endings in the tumor cells is unusual in that no such observation has been previously recorded in a case of cardiac rhabdomyoma. Oertel, Nye and Thomlinson [6] demonstrated a nerve supply and nerve endings in tumor cells in many types of benign and malignant tumors, including myoma. Their conclusions are "that mature and immature human tumour tissues are innervated, and that this

6. Oertel, H.; Nye, H., and Thomlinson, B.: J. Path. & Bact. **34**:661, 1931.

innervation applies to blood vessels and also to the stroma and parenchma of the growing tumour. We found this conception upon the close coordination of newly-formed nerve fibres with stroma and parenchyma in which they end, and to whose cells and nuclei they are so intimately attached that a resemblance to normal innervation is definitely noticeable. *In tumours as in other tissue movements, the advance occurs as tissue entity, not in isolated parts.*"

The small nodules in both kidneys were composed of cells somewhat resembling those of the primary cardiac rhabdomyoma. Karsner[7] recorded the fact that "heterologous rhabdomyoma occurs in situations where striated muscle is not normally present as in the kidneys, testes, other parts of the genito-urinary tract, oesophagus, parotid gland and elsewhere."

Cerebral cortical atrophy and accompanying glial sclerosis have been observed in other cases of cardiac rhabdomyoma. However, owing to the complicating factor of syphilitic meningoencephalitis, we are unable to state definitely that the cerebral changes were in any way connected with the cardiac rhabdomyoma.

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7. Karsner, H. T.: Human Pathology, ed. 4, Philadelphia, J. B. Lippincott Company, 1934, p. 382.

SYPHILIS OF PUEBLO SKULL BEFORE 1350

HENRI STEARNS DENNINGER, M.D., GLENDALE, ARIZ.

Syphilis in the form of prehistoric bone lesions has during the past several years demanded considerable recognition in the field of paleopathology. The report of the extensive investigation made by Williams [1] has been largely responsible for the study of this disease in the skeletal material in the various museums in North and South America. Williams described many specimens which present almost indubitable evidence of the occurrence of syphilis in this hemisphere before 1500 A. D. Soon after this report, I had the opportunity of presenting a case of prehistoric syphilitic periostitis.[2] More recently Krumbhaar [3] described an example of pre-Columbian syphilitic periostitis found in Peru, in which he demonstrated histologic structures and cells in the desiccated bone marrow.

I now report another specimen showing prehistoric syphilis, with definite chronologic data.

The skull now described (Tuzigoot II-50) was obtained during the excavation of the Tuzigoot ruin, a prehistoric pueblo burial site near Clarkdale, Ariz. The work of excavation, carried on as a CWA project during 1933 and 1934, was supervised by L. R. Caywood and E. H. Spicer, of the University of Arizona under the direction of Byron Cummings, director of the Arizona State Museum.[4]

Tuzigoot is a late pueblo site, probably first occupied shortly before 1000 A. D. and abandoned shortly after 1350 A. D. During this time, as both artefacts and architectural features indicate, there was a fluctuating population for the pueblo. The ruin occupies the top of a small but sharply elevated ridge of land, and the burials were made along the sides and bottom of the ridge in such proximity to the pueblo and containing such associated artefacts that their contemporaneity with the pueblo is beyond dispute.

The number of the burials encountered was large, something over 400, but the conditions for preservation had been poor and posthumous disturbance had been frequent, so that it was possible to save only a small percentage of the skeletal material for laboratory study.[5] No other remains of II-50 than those described here are available for examination.[6]

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1. Williams, H. U.: Arch. Path. **13**:779 and 931, 1932; Arch. Dermat. & Syph. **33**:783, 1936.

2. Denninger, H. S.: Southwestern Med. **19**:202, 1935.

3. Krumbhaar, E. B.: Ann. M. Hist. **8**:232, 1936.

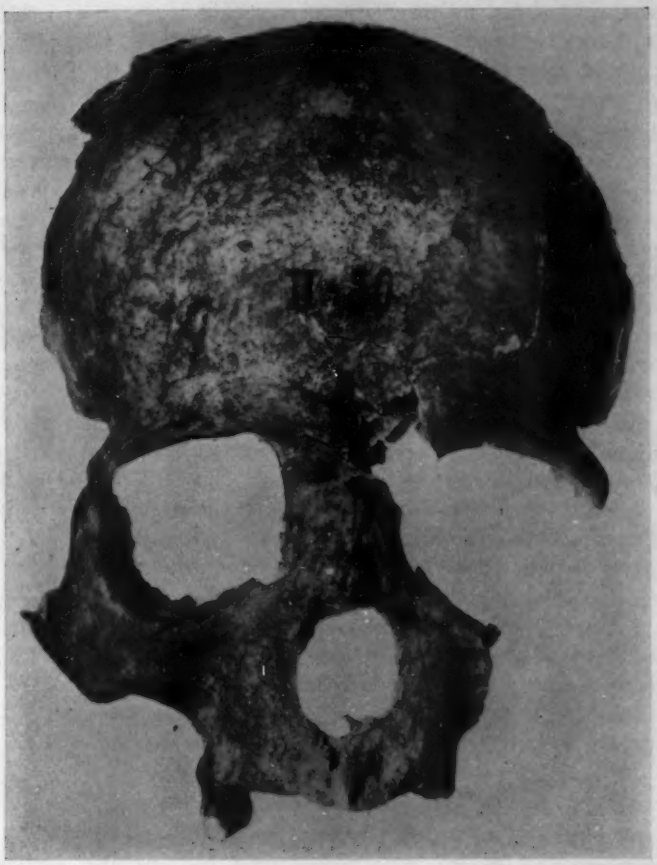
4. For a report of the excavation see Caywood, L. R., and Spicer, E. H.: Tuzigoot: The Excavation and Repair of a Ruin on the Verde River Near Clarkdale, Arizona, Tucson, Thesis, University of Arizona, 1935.

5. The skeletal material was the subject of a comparative anthropometric study by Helen M. Forsbery in 1934-1935 (Skeletal Remains from Kinishaba and Tuzigoot, Thesis, University of Arizona, 1935).

6. Dr. John Provinse, of the University of Arizona, supplied the archeologic data used in this report.

DESCRIPTION OF SKULL

The remains of burial II-50 are represented only by the facial bones and the upper portion of the cranium. The surface of the frontal bone is smooth but over the frontal eminences it contains symmetric diffuse swellings which extend upward to the coronal suture. This portion of the frontal bone appears to be somewhat thicker than normal, but no pathologic change in the spongy bone of the



Photograph of the anterior aspect of the skull (Tuzigoot II-50), made by Dr. Emil W. Haury.

diploic space or of the inner or outer bone plate is apparent. The most prominent pathologic feature is to be noted around the nasal region of the skull. The sharp nasal margin of the maxilla of each side is eroded and smoothed off in a rather hard, dense ring of bone. In the upper portion, at the junction of the nasal portion of the maxilla with the nasal bones, there is on each side an overgrowth with lipping. The nasal bones present at their tips a smooth but irregular pathologic bone formation with deformity. The nasal aperture, in contrast to the normal

elongated oval shape, definitely presents a round, punched-out, ulcer-like contour. The nasal spine is also eroded away.

The nasal bones show evidence of previous caries and necrosis, which has been followed by osteoplastic cicatrization and bone deposition. The nasal bones appear to have a marked increase in the concave curvature as viewed anteriorly. There is a complete continuous bony union between the nasal bones themselves and at the nasofrontal and nasomaxillary articulations.

The anterior faces of the maxillary bones present a rough, irregular, eroded surface with small eburnated confluent deposits, a condition which is obviously an extension of the nasal lesions. This is most marked on the inferior margin of the left orbit.[7]

The frontal process of the left maxillary bone is also involved by the sclerotic changes and is considerably thickened in the region of the lacrimal canal.

Unfortunately that portion of the nasal cavity containing the ethmoids was destroyed while in the ground. However, a sufficient portion of the right middle turbinate remains to indicate that it also was involved by a destructive process and subsequently underwent bony induration. Most regrettable is the mutilation of the palate, which occurred through accident when the skull was on exhibition. The palate contained a perforation about 1.5 cm. in diameter, approximately centered in the midline behind the foramen incisivum. The edges of the perforation were rounded with an indurated ring of bone.[8]

The upper jaw is essentially edentulous except for the first right molar, which incidentally shows evidence of apical abscesses. The lower jaw is missing. The age of this person must be estimated only from the portion of the skull which is in hand. After a careful consideration of the edentulous upper jaw with its single remaining molar, which shows evidence of considerable wear, I should roughly place the age around 50 or 60. The sex is indeterminate.

Roentgen examination of the skull reveals the circular nasal opening, the increase in density in the left frontal process of the maxillary bone and to some extent the fusion of the nasal bones with the adjacent structures. The frontal bone presents numerous fine cracks, which are artefacts, probably due to changes in temperature and in moisture since burial. Under these circumstances I do not believe that the finely mottled appearance of the frontal bone is at all significant.

SUMMARY

A skull is described which presents destruction of the bones of the nasal aperture and cavity, with subsequent healing and cicatrization, a similar process involving the nasal and maxillary bones, resulting also

7. Williams, H. U.: Arch. Path. **13**:779 and 931, 1932. Williams here described and illustrated several specimens presenting nasal and palatine lesions which are typical of syphilitic involvement. It will be noted that in most of the specimens illustrated there is also involvement of the frontal bone.

8. I saw this perforation of the palate when I originally examined this specimen at the University of Arizona about a year ago. Unfortunately, the accident occurred before the arrangement for making pictures of this defect had been completed.

in marked deformity, which probably produced a typical "saddle nose," and perforation of the palate with eburnated bony edges. The diagnosis of syphilis seems to be justified. On the basis of the archeologic data, this specimen may be placed between the years 1000 and 1350 A. D.

Laboratory Methods and Technical Notes

A COMBINED GRAM-METHYL GREEN-PYRONINE STAIN FOR FORMALDEHYDE-FIXED TISSUE

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Since the publication of the preliminary report of a gram–methyl green–pyronine stain [1] applicable to formaldehyde-fixed tissue the manufacture of the dyes has been improved and the technic simplified. The advantages of this method of staining are that it combines the results obtained by Gram's method with the cellular differential features of the Unna-Pappenheim stain, is carried out with easily procured American dyes of consistent composition in stable aqueous solutions and is rapid and simple.

TECHNIC

Paraffin sections of tissue fixed in 10 per cent solution of formaldehyde U. S. P. are prepared as usual for staining.

1. Stain with crystal violet solution for five minutes. Wash thoroughly.
2. Place in alkaline iodine solution for five minutes. Wash.
3. Decolorize with pure technical acetone. Wash.
4. Stain with methyl green–pyronine solution for from one to two minutes. Wash.
5. Decolorize with acetone, clear in two changes of xylene and mount in balsam.

PREPARATION OF SOLUTIONS

Crystal violet, 1 Gm., is dissolved in 10 cc. of buffer phosphate solution of p_H 6.6 to 7 and diluted to 100 cc. with distilled water.

Resublimed iodine, 2 Gm., is added to 10 cc. of normal sodium hydroxide diluted to 30 cc. The iodine solution is shaken frequently and gradually diluted to 100 cc.

In a flask is placed methyl green, 0.65 Gm., and a special pyronine, 0.1 Gm. Hot distilled water, 100 cc., is added to the dry dyes and the solution allowed to stand for from three to four days before being used. It is stored in a well stoppered amber glass bottle. The methyl green used is more highly ethylated than the usual grade and has a dye content of 65 per cent. The pyronine is a special yellow pyronine.[2]

All the solutions can be made up in bulk, since they are stable. In this laboratory, at present, they are made up in 3 liter volumes. When the larger amounts are prepared, only the first half of the distilled water used in dissolving the methyl green and pyronine needs to be heated.

From the Pathological Laboratory, City Hospital, Welfare Island, Department of Hospitals of the city of New York.

1. Scudder, S. A., and Lisa, J. R.: Stain Technol. **6**:51, 1931.

2. Both these dyes are manufactured by the National Aniline & Chemical Company, New York. The methyl green is marketed under the name Methyl Green N G 10; the pyronine, as "pyronin yellow special."

COMMENT

The length of staining is important. Not less than five minutes is necessary for both the crystal violet and the iodine. A shorter time tends to cause uneven staining of the gram-positive organisms, resulting in inaccurate observations. A short period only is advisable for the counterstaining, from one to two minutes. It is occasionally better to dilute the counterstain, particularly when the cellular exudate is dense. The dilution can be modified to suit the particular requirement for depth of color.

The acetone must be of an excellent grade; any impurity vitiates the results, particularly in regard to the counterstain. After the first decolorization, the acetone should be washed off quickly, without allowing the tissue to dry. Decolorization of the counterstain must be carried out promptly after washing. If the slide is allowed to stand in water, the counterstain tends to become homogeneous in color, and the differential characteristics are lost. This does not apply to the washing after staining with iodine, since allowing the slide to stand in water several minutes causes no difficulty. After the second decolorization, plunging the slide into xylene as soon as the tissue dries facilitates clearing.

RESULTS

Gram-positive bacteria stain deep purple-black. Gram-negative bacteria stain magenta. The neisserian organisms particularly stain brilliant deep magenta. Tubercle bacilli do not stain, but lepra bacilli stain like other gram-positive bacteria. Capsules either are unstained or faint lavender. Polymorphonuclear cells have nuclei varying from dark purple to green-blue; their cytoplasm shows a faint, finely granular lavender. Small lymphocytes have dark navy blue nuclei and an unstained or faintly magenta cytoplasm. The nucleus of the plasma cell is dark navy blue, with a cartwheel arrangement of the chromatin; the cytoplasm shows a homogeneous deep magenta except in a clear perinuclear zone. The eosinophils have nuclei similar to those of the polynuclear cells; the granules stain somewhat unevenly reddish or purple. The granules of the mast cells stain like gram-positive cocci but are easily distinguished by their homogeneous shape and their arrangement, obscuring the nucleus. Endothelial cells have very pale blue, delicate nuclei. Giant cells of the Langhans type have nuclei similar to that of the endothelial cell; their cytoplasm stains like that of the plasma cell. The Aschoff cell is similar. Erythrocytes are bronze to yellow.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—A. L. Joyner succeeds H. K. Fidler as assistant professor of bacteriology and pathology at the University of Alabama.

T. A. Gonzales, associate professor of forensic medicine, has been promoted to be professor of forensic medicine at New York University.

John Musser Pearce, formerly of the Rockefeller Institute for Medical Research, Princeton, N. J., has been appointed instructor in pathology at the Long Island College of Medicine.

Caspar G. Burn, formerly assistant professor of pathology at Yale University Medical School, has been appointed associate professor of pathology at the Long Island College of Medicine. He is to be in charge of the pathologic service recently established by the school at the Kings County Hospital.

At the Ottawa meeting of the American Association for the Advancement of Science the Theobald Smith Award in Medical Science was given to Charles F. Code, of the Mayo Foundation, for his work on histamine in the blood.

Max Pinner, Oneonta Tuberculosis Hospital, New York, has been appointed chief of the division of pulmonary diseases in Montefiore Hospital for Chronic Diseases, New York.

Ralph Mosteller, pathologist, Spartanburg General Hospital, Spartanburg, S. C., has been appointed director of the division of cancer control of the Georgia state department of health, succeeding J. W. Schereschewsky.

James B. Murphy, of the Rockefeller Institute for Medical Research, New York, has been awarded the honorary degree of Doctor of Science by Oglethorpe University, Atlanta, Ga.

Earl Baldwin McKinley, dean and professor of bacteriology and director of medical research at the George Washington University School of Medicine, Washington, D. C., and president of the American Association of Pathologists and Bacteriologists, and Fred Campbell Meier, plant pathologist of the United States Department of Agriculture, were on the Hawaii Clipper, lost over the Pacific, July 28, 1938. They were engaged in research on aerobiology and in making arrangements for the continuation of the collection of micro-organisms, viruses, pollens and dust in the upper air by officers of the trans-Pacific airships.

Society News.—The forty-ninth annual meeting of the Association of American Medical Colleges will be held at Syracuse, N. Y., Oct. 24, 25 and 26, 1938.

Awards.—Florence B. Seibert, of the Henry Phipps Institute, of the University of Pennsylvania, was awarded the Trudeau Medal by the National Tuberculosis Association, at its recent meeting, for distinguished research on the tuberculin test.

Benjamin T. Terry was awarded the gold medal for his exhibit on the early diagnosis of cancer at the recent meeting of the American Society of Clinical Pathologists in San Francisco.

Peyton Rous, of the Rockefeller Institute for Medical Research, has received an honorary degree at Cambridge University in England.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Experimental Pathology and Pathologic Physiology

Dynamic Effect of Acute Experimental Poisoning of the Heart with Diphtheria Toxin. D. B. Witt, E. Lindner and L. N. Katz, Am. Heart J. **13**:693, 1937.

The acute effect on the cardiac dynamics of injected diphtheria toxin was studied in dogs. The study was based on records of mean arterial and venous blood pressures and records of the volume and pressure changes of the heart. Electrocardiograms were obtained also. The pressure curves of the various chambers of the heart (i. e., the two ventricles, the pulmonary artery and the aorta) were recorded with Wiggers' manometers on a photokymograph. The volume and mean pressure curves were obtained on a smoked drum. It was found that the diphtheria toxin produced a sinusal slowing of the heart and later various types of atrioventricular and intraventricular block. Extrasystoles of various types and paroxysmal tachycardia also were present, and eventually the heart went into a peculiar type of ventricular fibrillation which the authors describe. Vasodilatation in both the systemic and pulmonary circuits also resulted. Heart failure was caused by these disturbances in conduction and rhythm and by the decrease in coronary blood supply following systemic vasodilatation. There was definite evidence, however, that diphtheria toxin poisoned the heart in such a way that myocardial failure, with its typical abbreviated and less powerful contraction, occurred sometimes before these other changes came into operation. There was evidence also of a loss of tone in the ventricles toward the end. It is of practical importance to realize that diphtheria toxin acts directly on the contractile power and tone of the heart, since serious damage to the heart may be present or may develop quickly before significant modification of the electrocardiogram or of blood pressure is observable.

From Authors' Summary.

Dietary Nephritis in the Rat. E. M. Medlar and N. R. Blatherwick, Am. J. Path. **13**:881, 1937.

It has previously been shown that when rats are fed certain diets high in animal protein progressive chronic degenerative nephritis can be produced consistently. The pathogenesis of this nephritis is considered here. It appears that the initial lesions are focal injuries in the filter beds of the glomeruli and that they are progressive. Subsequent to the glomerular damage occur injury, hyperplasia and dissolution of the tubular epithelium of the glomerular capsule, loops of Henle and distal convoluted tubule. The end result is chronic degenerative nephritis in which the principal features are: sclerosis of glomeruli, with or without obliteration of the capsular spaces; interstitial fibrosis in the regions of the tubule where the epithelium has been seriously affected; chronic inflammation, which may be considerable, and cystic dilatation of the proximal convoluted tubules, which may or may not be extensive. The possible relation of experimentally produced dietary nephritis to the chronic nephritides in general is briefly discussed. A suggestion is ventured that chronic degenerative nephritis in general may depend primarily on an irreparable damage to the filter bed of the kidney and that the etiologic factors initiating this primal damage may be multiple and diverse. The authors are of the opinion that it is inadvisable to attempt to designate the origin or nature of the etiologic agents that induce progressive degenerative changes in the kidney, since information pertaining to the complex phenomenon is so incomplete.

From Authors' Summary.

PRODUCTION OF HYALINE ARTERIOSCLEROSIS AND ARTERIOLONECROSIS BY MEANS OF PROTEOLYTIC ENZYMES. A. R. RICH and G. L. DUFF, Bull. Johns Hopkins Hosp. **61**:63, 1937.

Arteriolar lesions having the characteristics of human hyaline arteriolosclerosis and arteriolonecrosis occur at the sites of injection of tryptic enzymes of animal or plant origin (pancreatic juice, commercial or crystalline trypsin, papain). Complete necrosis and hyalinization of the walls of vessels can occur within twenty-four hours. Neither previous medial hypertrophy nor intimal proliferation is essential for the thickening of the affected wall with consequent narrowing of the lumen. These changes can take place, apparently by inhibition, within twenty-four hours. Whether the proteolytic enzymes act directly on the wall or whether the lesion results from the action of products of protein decomposition is at present undetermined.

FROM AUTHORS' SUMMARY.

OBSERVATIONS ON INTERMEDIN. D. LEWIS, F. C. LEE and E. B. ASTWOOD, Bull. Johns Hopkins Hosp. **61**:198, 1937.

The work of Zondek and Krohn on the concentration of intermedin in the hypophyses of cattle was repeated with some modifications. Values were obtained which were from five to twenty times as great as those reported by those investigators. The yellow puslike material in the cleft gave the highest average values, being closely followed by the pars intermedia. This exudate in the cleft consisted of desquamated cells from the walls of the cleft, chiefly from the pars intermedia. The colloid material in the cleft showed a lower concentration. The hypophysial stalk and the region about the third ventricle of the brain contained progressively less intermedin the further from the pituitary gland the samples of tissue were taken. The capsule of the gland contained intermedin, but the cavernous sinus did not. It is probable that diffusion is responsible for these various concentrations. Because of the absence of typical basophilic cells in the pars intermedia of the hypophysis of cattle, as judged by the use of Spark's stain, it is believed that intermedin is not formed by these cells.

FROM AUTHORS' SUMMARY.

THE EFFECT OF DIET ON THE SUSCEPTIBILITY OF THE CANINE HEMATOPOIETIC FUNCTION TO DAMAGE BY AMIDOPYRINE. D. K. MILLER and C. P. RHOADS, J. Exper. Med. **66**:367, 1937.

By feeding dogs a black tongue diet and at the same time administering aminopyrine, acute stomatitis and anemia may be produced. Both stomatitis and anemia occur some time before they could be expected to appear as a result of the feeding alone. The anemia is associated with suppression of maturation of the hemopoietic elements of the bone marrow.

FROM AUTHORS' SUMMARY.

STUDIES ON PULMONARY EDEMA. S. FARBER, J. Exper. Med. **66**:397 and 405, 1937.

Bilateral cervical vagotomy in rabbits soon leads to death, usually within from eight to twenty-four hours. The important clinical features are gradually increasing dyspnea, crises with expulsion of frothy serous or sanguineous fluid from the mouth and nose and terminal asphyxia. Postmortem examination reveals severe acute pulmonary edema and congestion, bronchopneumonia in variable amounts and evidences of aspiration of food and of secretions. This picture is similar to that found in the lungs in the bulbar form of poliomyelitis. These changes are brought about by a combination of factors secondary to bilateral vagotomy, namely, laryngeal paralysis (aspiration of food, slow asphyxia) and loss of the vagal innervation of the lungs. Laryngeal paralysis is not an essential factor in the production of severe pulmonary edema and death following bilateral cervical vagotomy. To denote the pathogenesis of this type of edema, the term "neuropathic pulmonary edema" is employed.

Guinea pigs die shortly after bilateral cervical vagotomy, even when continuous artificial respiration, effected through a tracheal cannula, is carried out. Death is caused by severe pulmonary edema and congestion. Direct observation of the lungs after bilateral vagotomy demonstrates that pulmonary edema develops gradually and increases slowly in amount and severity. Congestion precedes and accompanies the development of the edema. Neuropathic pulmonary edema in the guinea pig is caused by disturbance to, or abolition of, the pulmonary vasomotor nerves. The evidence obtained by experiments on animals suggests that neuropathic pulmonary edema in man is caused by disturbances, either central or peripheral, in the vasomotor control of the pulmonary vessels.

FROM AUTHOR'S SUMMARIES.

ABSORPTION OF PROTEIN SOLUTIONS FROM THE PULMONARY ALVEOLI. C. K. DRINKER, M. F. WARREN and M. MACLANAHAN, J. Exper. Med. **66**:449, 1937.

Horse serum, crystallized hemoglobin and crystallized egg albumin were injected into the pulmonary alveoli of dogs in which the entrances to the lymphatics on the right had been tied and the thoracic duct cannulated. Following this injection, samples were taken of blood and lymph. The horse serum and hemoglobin were detected by immunologic methods only after several hours and invariably appeared first in the blood. Egg albumin also entered the blood capillaries but much more rapidly than the other two proteins, probably owing to the smaller molecular size.

FROM AUTHORS' SUMMARY.

REGENERATION OF SERUM PROTEIN. D. MELNICK and G. R. COWGILL, J. Exper. Med. **66**:493 and 509, 1937.

When the dog is subjected to quantitative plasmapheresis and fed appropriate synthetic artificial rations, it is possible to evaluate the ability of the organism to regenerate serum protein from both exogenous and endogenous sources. Approximately 44 per cent of the protein (casein) fed in excess of the minimal amount needed normally to meet the general nitrogen requirements is utilized for the formation of new serum protein. Under the authors' experimental conditions the dog can regenerate each week solely from endogenous sources approximately 0.6 Gm. of this blood protein per kilogram of optimal body weight. This is equivalent to about 21 per cent of the serum protein normally present in the plasma. When the dog is fed a diet containing an adequate amount of protein and is subjected to prolonged intensive plasmapheresis (over a period of sixteen consecutive weeks), no impairment in its ability to regenerate serum protein from either exogenous or endogenous sources occurs. Under these conditions of experimentation the dog appears to be able to form each week blood protein in an amount approximately equal to that normally present in the plasma. Because of this remarkable ability, it seems that in Bright's disease loss of protein alone cannot be responsible for the persistent hypoproteinemia. An additional factor, the specific ability of the patient to regenerate serum protein, must be taken into consideration.

In view of the short period of gestation in this species and in view of the relatively large litter that is produced and nursed, the dog, compared with the human being, undergoes a much greater physiologic strain during pregnancy and lactation. This is evidenced by marked decreases in the hematocrit values, in the total cell volumes and in the serum protein concentrations, by an appreciable hydration of the plasma and in some cases by significant reductions in the total circulating serum protein. When pregnant dogs are fed a protein-free diet, the caloric intake being at a high level, and are subjected to the authors' standardized technic of plasmapheresis, it is possible to deplete the animals of their reserve serum protein stores and to reduce the serum protein concentration to the basal level (from 3.5 to 4.2 per cent) within the extremely short period of from two to three days.

This indicates that the dog during pregnancy possesses a limited amount of reserve serum protein. Once the basal level of the serum protein is attained, the pregnant or lactating dog exhibits marked impairment in its ability to regenerate serum protein. The synthesis of body proteins in the fetus during lactation is considered to be an internal plasmapheresis, leading to depletion of the maternal serum protein by preferential utilization of the materials from which this complex is made. These parasitic effects on the maternal organism are believed to be of primary importance, over and above any hydremia, in causing the decrease in serum protein concentration characteristic of pregnancy.

FROM AUTHORS' SUMMARY.

EXPERIMENTAL ANEMIA PRODUCED BY EGG WHITE IN RABBITS. M. MILLET, Arch. internat. de méd. expér. **12**:437, 1937.

Rabbits were given by subcutaneous injection an emulsion of egg white in doses of from 2 to 10 cc., the total amount received by the animals varying from 10 to 160 cc. The animals became anemic and showed induration and congestion of the spleen and apparent hyperplasia of the marrow. Perl's reaction often showed marked siderosis of the spleen. Hemosiderin granules in varying amounts were found in a number of cells of the reticulum of the pulp and the endothelium of the sinuses. Other cells contained pigment in a diffuse state. The amount of this pigmentation was in direct proportion to the length of the experiment and the degree of anemia. A number of macrophages containing varying amounts of hemoglobin were recognized. In comparison with the spleen, the marrow presented a much more pronounced hemosiderosis, at least in those cases in which it had reacted to the anemia with intense and prolonged reticulocytosis. The marrow presented a picture of active regeneration and hyperplasia, with little remains of the rarefied adipose tissue but, in comparison, numbers of nucleated erythrocytes. In cases in which the splenic siderosis was intense, the kidneys and liver also contained pigment.

I. KAWASAKI.

Pathologic Anatomy

CYSTIC TUMOR OF THE THIRD VENTRICLE CONTAINING COLLOID MATERIAL. H. ZEITLIN and B. W. LICHTENSTEIN, Arch. Neurol. & Psychiat. **38**:268, 1937.

A study of 2 cases of so-called cystic tumor of the third ventricle convinced the authors that such tumors originate from the paraphysis, a structure which arises from the most rostral portion of the roof of the third ventricle and which may be identified in human beings, but only in embryos. One of the tumors measured 5 by 4.5 by 3.5 cm. and the other 30 by 25 by 25 mm. Both exhibited an identical structure: a homogeneous mass contained within a connective tissue capsule, the inner surface of which was lined by a single layer of cuboid epithelial cells, mostly flattened. The capsule contained numerous tubules, which were lined with cells similar to those of the capsule. The structure of the capsule generally much resembled that of the paraphysis, and for this reason Zeitlin and Lichtenstein prefer the name "paraphysial cyst" to "colloid cyst" or "neuroepithelial cyst."

GEORGE B. HASSIN.

PATHOLOGIC FEATURES OF MULTIPLE SCLEROSIS AND ALLIED CONDITIONS. G. B. HASSIN, Arch. Neurol. & Psychiat. **38**:713, 1937.

The main pathologic features of multiple sclerosis are not so much patches as defects in the myelin, which may be detected throughout the brain, spinal cord and nerve roots, even in areas appearing apparently normal (when stained by the Weigert-Pal method or its modifications). With the use of the silver and especially the nuclear staining methods (toluidine blue, thionine, hematoxylin-eosin) it is possible to demonstrate degenerative and reactive glial changes even in very early

stages of the disease. Degeneration involves the nerve fibers of the brain, of the spinal cord and partly of the nerve roots; it spares the ganglion cells. The latter may become affected secondarily (in long-standing cases); changes in the glia, blood vessels and meninges are always secondary. Inflammatory phenomena (infiltration by lymphocytes and plasma cells), if present, are a manifestation of a so-called sympathetic or secondary inflammation. Primary degeneration of nerves occurs also in other morbid conditions, such as Schilder's disease, neuro-optic myelitis and postvaccinal or postmeasles encephalomyelitis, but it runs a rapid course. The reactive changes are mesodermal and not glial, and the changes in the glia are regressive, not progressive, as in multiple sclerosis. Such morbid conditions have been improperly termed acute, subacute or malignant multiple sclreosis. In the author's opinion they belong with what was described by Bassoe and him as multiple degenerative softening, in which the softening (acute degeneration of nerve fibers) is due not to vascular disturbances but to the direct effect of some toxins on the parenchyma of the nerve fibers, causing their rapid degeneration.

AUTHOR'S SUMMARY.

LESIONS OF LEAD ENCEPHALITIS IN CHILDREN. S. S. BLACKMAN JR., Bull. Johns Hopkins Hosp. **61**:1, 1937.

Pathologic study of 22 cases of lead encephalitis in children showed lesions distributed throughout the entire nervous system, especially in the cerebral hemispheres and in the cerebellum. The dominant microscopic change was serous inflammation associated with necrosis of capillaries and thrombi, tissue damage and evidence of repair. Most of the injury to the nervous tissue was due to the accumulation of exudate, consisting of serous fluid without fibrin, which collected about the blood vessels and in the meninges and in some cases permeated large fields of brain tissue. Often the exudate was found in the gray matter about the capillaries as small droplets, which after a lapse of weeks or years became basophilic, accumulated iron and stained like calcium. This exudate caused distortion of the architecture of the brain through tearing and necrosis of nerve fibers and glial cells in both gray and white matter, resulting in small perivascular hemorrhages and focal areas of necrosis. These lesions were evident in the molecular layer, in the Purkinje cell layer and in the dentate nucleus of the cerebellum and were scattered at wide intervals in the basal nuclei, brain stem, pons, medulla and spinal cord. In these areas there were small rosettes of glial cells about necrotic nerve cells, foci of necrotic tissue and nodules of neuroglial cells and fibers replacing damaged tissue. The changes in the choroid plexuses, retinas, optic nerves, pineal gland and hypophysis were slight.

FREDERICK STENN.

SIGNIFICANCE OF THE INCREASED FREQUENCY OF SELECTIVE CORTICAL NECROSIS OF ADRENALS AS A CAUSE OF ADDISON'S DISEASE. H. G. WELLS, E. M. HUMPHREYS and E. G. WORK, J. A. M. A. **109**:490, 1937.

A woman aged 57 died the second day after her admission to the hospital with a diagnosis of pemphigus vulgaris, with which she was known to have been afflicted for over a year. The autopsy showed extensive pemphigic lesions of the skin and of the oral mucosa. There was no noticeable cutaneous pigmentation. Each adrenal showed atrophy of the cortex with a normal medulla. Microscopically, there was destruction of the adrenal cortical parenchyma without evidence of regeneration. Outside the adrenal capsule there was a small accessory nodule of cortical tissue with the same degenerative changes. In the other organs the changes were not significant. This occurrence of selective cortical necrosis of the adrenal was correlated with the administration of germanin to the patient. Germanin, also called Bayer 205, is a carbamide of meta-aminobenzoyl-meta-amino-paramethylbenzoyl-1-naphthylamine-4, 6, 8-trisulfonic acid, mostly known for its trypanocidal effect; it has also been known to have hemotoxic, hepatotoxic, myelotoxic and particularly strong nephrotoxic effects. Wells and associates produced,

with proper dosage, selective damage in the kidneys and adrenals of guinea pigs. In a few of the animals the damage in the adrenal cortex was more marked than that in the liver. Large doses produced severe damage in the kidneys, liver, myocardium and adrenal glands of rabbits and guinea pigs. That the pemphigus was not responsible for the lesion in the adrenals is concluded from the observations at autopsy recorded in the literature on that disease. Wells and his associates suspect that in some of the cases of selective damage to the adrenal cortex, chemicals may be responsible. In recent years selective destruction of the adrenal cortex seems to be observed more frequently than formerly as the cause of Addison's disease. This is evidenced by the fact that until a few years ago nearly all cases of Addison's disease were the result of tuberculosis of the adrenals, whereas, of the last 16 cases in the Billings Memorial Hospital, Chicago, 9 were due to "selective destruction of the adrenal cortex." I. DAVIDSOHN.

ENDOMETRIOSIS OF THE COLON AND RECTUM WITH INTESTINAL OBSTRUCTION. R. B. CATTEL, New England J. Med. **217**:9, 1937.

The 104 instances of endometriosis considered in this paper fall into three groups: (1) rectovaginal endometriosis, (2) diffuse involvement of the sigmoid and rectum and (3) discrete endometrioma of the sigmoid. Endometriosis of the sigmoid, colon or rectum may lead to intestinal obstruction. A preoperative diagnosis is seldom made, but endometriosis should be suspected in cases of long-standing obstruction with aggravation at the time of menstruation and accompanied by pelvic symptoms. DAVID H. WAGNER.

RECURRING MYXOMATOUS CUTANEOUS CYSTS OF THE FINGERS AND TOES. R. E. GROSS, Surg., Gynec. & Obst. **65**:289, 1937.

The condition is uncommon. It is characterized by recurrent formation of a small myxomatous cyst of the skin of a finger or of a toe, not lined by a secretory epithelial membrane and not originating from an adjacent joint cavity, bursa or tendon sheath. The lesion is degenerative and is produced by a peculiar mucoid change in the connective tissue of the corium that goes on to liquefaction and formation of a cyst. The cause is unknown, but local trauma may play a rôle. The author records 22 examples, 8 of which he studied. Of these, all but 1 were situated on fingers. These cysts varied in diameter from a few millimeters to slightly more than a centimeter. The site was commonly the dorsal aspect of a distal interphalangeal joint and usually a little to one side of the midline. The cysts were thin walled and contained a colorless glairy mucoid or gelatinous fluid. Three fourths of the subjects were women. The average age of the patients was 48 years. Such lesions are resistant to surgical forms of therapy, tending to recur again and again, but yield to irradiation with radium or roentgen rays.

FROM AUTHOR'S SUMMARY. (WARREN C. HUNTER.)

OSTEOPOROSIS IN A RABBIT. J. W. ORR, J. Path. & Bact. **45**:29, 1937.

The accidental observation in an adult male rabbit of a condition resembling Paget's disease of bone (osteitis deformans) is recorded. The entire skeleton was affected, the bones being softened, thickened and porous and of approximately normal calcium content. FROM AUTHOR'S SUMMARY.

PROLIFERATION OF LYMPHATICS IN INFLAMMATION. B. D. PULLINGER and H. W. FLOREY, J. Path. & Bact. **45**:157, 1937.

From the present and other studies it is clear that current descriptions of the reactions occurring in injured tissues should be expanded to include the lymphatics on the same footing as the blood vessels. Lymphatic proliferation may well be as important for successful repair as proliferation of the blood vessels.

FROM AUTHORS' SUMMARY.

POSTPARTUM NECROSIS OF THE ANTERIOR PITUITARY. H. L. SHEEHAN, J. Path. & Bact. **45**:189, 1937.

A description is given of 11 cases of recent necrosis of the anterior lobe of the pituitary in women dying soon after obstetric delivery and of a case in which the woman survived a similar necrosis for eighteen months but died after her next delivery. From a consideration of these cases and of those described in the literature the following conclusions are drawn: 1. Necrosis of the anterior lobe of the pituitary is frequently observed in women dying during the puerperium. 2. The necrosis begins about the time of delivery. 3. It is due to thrombosis of pituitary vessels, not to embolism. 4. The thrombosis is usually consequent on the collapse of the patient following severe hemorrhage at delivery, often as a result of retention of the placenta. 5. Puerperal sepsis is commonly associated with the condition but is not of proved etiologic importance; it is more probably a subsequent complication. 6. If the patient survives the puerperium, the lesion heals to a mass of condensed stroma, which in most cases contains a few islets of healthy parenchyma in certain constant situations. This is the stage found in the cases of Simmonds' disease in which the condition dates from a delivery some years earlier. The histologic appearances are usually easily distinguishable from those of the fibrosed pituitaries found in certain of the cases of Simmonds' disease in which the condition does not follow delivery. FROM AUTHOR'S SUMMARY.

CYSTIC LATENT MASTOPATHY. F. FRANZAS, Arb. a. d. path. Inst. d. Univ. Helsingfors **9**:401, 1936.

This is a study of cystic changes in the breasts of 100 women from 19 to 80 years of age. The history of, and the literature on, the subject and the different problems connected with it are thoroughly discussed and then analyzed on the basis of the author's material. For each case the essential and pertinent clinical data are given, followed by a brief summary of the observations at necropsy and of the gross and histologic changes in the breasts. Cystic mastopathy is clearly defined and differentiated from cystic changes due to obstruction in the larger ducts. It consists in cystic changes in the secretory terminal apparatus, with active epithelial proliferation or with columnar epithelium, or with evidences of such proliferation in the past. The cystic changes may also involve the terminal excretory ducts, with intracanalicular epithelial proliferation, provided that there are no dilatations of the large ducts that suggest retention as a possible factor in the formation of the cysts. Cysts that complied with the stated requirements were found in 55 per cent of the cases, and in 25 per cent they were bilateral. All these were latent, without clinical symptoms. The histologic differences between the cysts of cystic mastopathy and plain retention cysts are discussed in detail. Franzas does not believe that there is any relation between the connective tissue and cyst formation, and he states emphatically that there is no reason to consider this condition precancerous. A critical review of the available data compels him to conclude that the etiologic agent is hormonal: an abnormally differentiated hormone. It requires the presence of active epithelium in the breast. The differences in the ability of epithelium to respond account for the localization of the cystic changes. Cystic dilatation is secondary to epithelial proliferation. The presence of a loose or of a dense connective tissue or of fat around the acini are other factors.

I. DAVIDSOHN.

THE PHRENICOPLEURAL COLLATERAL CIRCULATION. H. H. KALBFLEISCH, Frankfurt. Ztschr. f. Path. **49**:10, 1936.

Kalbfleisch emphasizes the importance of adhesions between the visceral pleura and the diaphragm as a means for the production of collateral circulation in instances of long-standing occlusion of the pulmonary artery within the lower lobe of the lung combined with Laënnec's cirrhosis of the liver, as illustrated at postmortem examination in 2 cases.

L. OHRINGER.

A Postmortem Study of the Effects of Birth on the Central Nervous System of the Newborn. F. Hausbrandt and A. Meier, Frankfurt. Ztschr. f. Path. **49**:21, 1936.

The brains and the spinal cords of 103 of 138 infants who died shortly before or following delivery were examined. Tears in the tentorium cerebelli were three times as frequent in full term infants and intraventricular hemorrhages twice as frequent in the premature ones.

Damage of the spinal cord, usually present in the cervical region, was noted in 23 per cent of the cases. The authors stress the importance of examining the spinal cord in all cases in which examination of the remainder of the body fails to disclose the cause of the death.

L. Ohringer.

Thromboendarteritis Obliterans of the Pulmonary Arteries. F. Wiese, Frankfurt. Ztschr. f. Path. **49**:155, 1936.

Four instances are reported of thromboarteritis obliterans of small pulmonary arteries, which showed proliferation of the intima, accompanied by the formation of fibrinoid thrombi. Wiese believes that the resulting slowing of the circulation led to formation of thrombi and that in later stages the circulatory disturbances produced secondary pulmonary arteriosclerosis. It is assumed, since no signs of inflammation were present, that the endothelial cells were sensitized by some unknown agent. This sensitized endothelium provoked the formation of thrombi.

A. Strauss.

Eosinophilic Myocarditis. H. Šikl, Frankfurt. Ztschr. f. Path. **49**:283, 1936.

Šikl reports 3 instances of diffuse urticarial reaction after the use of bismuth and neoarsphenamine in the treatment of syphilis. This was followed by rapid cardiac decompensation and death. Post mortem, in every instance, a tremendous number of eosinophilic leukocytes and tubercle-like granulomas were found in the myocardium. Giant cells, probably of myogenic nature, were seen in 1 instance. Šikl regards this myocarditis as an allergic response to neoarsphenamine.

L. Ohringer

Pathologic Anatomy of Cushing's Disease. H. H. Kalbfleisch, Frankfurt. Ztschr. f. Path. **49**:337, 1936.

A typical case of Cushing's syndrome was observed in a man 53 years old. Post mortem there was demonstrated a pea-sized basophilic adenoma of the anterior lobe of the hypophysis, a small cortical adenoma of the adrenal and lipomatosis of a parathyroid gland. After a review of the literature, Kalbfleisch concludes that Cushing's syndrome is more closely related to the diencephalic region than to the hypophysis.

L. Ohringer.

Microbiology and Parasitology

Torula Infection. J. T. Crone, A. F. De Groat and J. G. Wahlin, Am. J. Cancer **31**:863, 1937.

A review of the literature on torulosis reveals that the purely visceral and local forms of the disease as opposed to the meningoencephalitic forms have been incompletely studied. Their frequency and course can be ascertained only by more complete laboratory studies. The experience of the authors with a case of generalized torulosis indicates the desirability of employing mice for inoculations as a routine. This belief is based on the great susceptibility of these animals and on the uniform and characteristic picture evoked. From this fact the authors suggest that intraperitoneal inoculation of mice should prove of value in establishing the etiologic diagnosis.

From Authors' Summary.

INTRANUCLEAR INCLUSIONS IN THE TISSUE REACTIONS TO FOREIGN SUBSTANCES. P. K. OLITSKY and C. G. HARFORD, Am. J. Path. **13**:729, 1937.

Intranuclear inclusion bodies resembling in certain important ways those found in virus diseases were induced in tissues by chemical substances, such as selected aluminum and ferric compounds and carbon, but not by others, such as barium sulfate, silver chloride and paraffin, and not by agar. No evidence was revealed of a virus infection in association with these inclusions. The results throw light on the interpretation of intranuclear inclusions as they occur in lesions caused by viruses.

FROM AUTHORS' SUMMARY.

MULTIPLICATION OF THE VIRUS OF YELLOW FEVER IN AËDES AEGYPTI. L. WHITMAN, J. Exper. Med. **66**:133, 1937.

The Asibi strain of the virus of yellow fever has been shown to be capable of multiplying in the bodies of Aëdes aegypti. After the mosquitoes have ingested infected blood, the content of virus in their bodies falls for several days, reaching a minimum during the first week. It then increases rapidly until quantities greater than those previously encountered can be demonstrated. The actual final amount of virus demonstrable, however, is subject to variations of which little is known.

FROM AUTHOR'S SUMMARY.

ELEMENTARY BODIES OF VACCINIA FROM INFECTED CHORIOALLANTOIC MEMBRANES OF DEVELOPING CHICK EMBRYOS. J. E. SMADEL and M. J. WALL, J. Exper. Med. **66**:325, 1937.

By a method of differential centrifugation and tryptic digestion suspensions of elementary bodies have been prepared from chorioallantoic membranes of chick embryos infected with vaccine virus. The infective titer of the final suspension of elementary bodies was usually the same as that of the original tissue emulsion. Elementary bodies from infected chick membranes were agglutinated by anti-vaccinal serum obtained from different mammalian species as well as were bodies prepared from inoculated rabbit skin. Seitz filtrates of infected chick material contained soluble precipitable substances of vaccinia; these filtrates and filtrates from infected rabbit skin, respectively, reacted equally well with rabbit serum which contained either L or S antibodies.

FROM AUTHORS' SUMMARY.

FATE OF LIVING BACTERIA INTRODUCED INTO THE UPPER PART OF THE RESPIRATORY TRACT OF THE RABBIT. P. R. CANNON and T. E. WALSH, J. Immunol. **32**:49, 1937.

Following intranasal instillation of suspensions of virulent cultures of staphylococcus aureus the staphylococci passed into the lungs; virulent pneumococci behaved similarly but later entered the blood stream from the lungs and not through the epithelium of the upper part of the respiratory tract. In animals previously vaccinated with killed bacteria in suspension the passage into the lungs of intranasally instilled pneumococci was not interfered with, but septicemia was prevented either by inhibition of the growth within the lungs or by inhibition of the passage from there to the circulation or by enhanced destruction in the liver, spleen and other tissues. India ink or trypan blue when instilled intranasally into rabbits and guinea pigs rapidly reached the lungs, where the distribution was determined by the mechanical factor of position.

I. DAVIDSOHN.

TOKYO AND ST. LOUIS ENCEPHALITIC VIRUS. M. KUDO and others, J. Immunol. **32**:129, 1937.

Mice were found to be equally susceptible to the Japanese B type and the St. Louis type of encephalitis when the virus was inoculated intracerebrally. The Japanese virus was more virulent when injected intraperitoneally and subcuta-

neously. The histologic changes in the brains were more pronounced in the animals dying from infection with the Japanese virus. Immune serums produced in rabbits by inoculations of brain suspensions had specific neutralizing properties. The immune serum against the St. Louis strain protected mice only against the homologous virus, while the serum against the Japanese strain had, in addition, marked protective properties against the St. Louis strain. The two viruses are apparently closely related though not identical.

I. DAVIDSOHN.

FURTHER OBSERVATIONS ON ROUGH CULTURES OF FUSIFORM BACILLI. R. TUNNICLIFF and C. HAMMOND, J. Infect. Dis. **61**:26, 1937.

These experiments indicate that small and large fusiform bacilli are stabilized but different forms of the same organism, the small developing into the large with dissociation from the smooth to the rough type and the large changing to the small forms with the R to S transformation. Their production of indole appears also to depend on the stage in the process of dissociation.

Horizontal sections of colonies containing the R factor when stained with either a modified Warthin or a Giemsa stain show an irregular lacy edge, in which spirilla-like forms predominate. The center of the colony is made up of short bacilli or filaments, depending on the degree of roughness of the colony. A stabilized rough culture has not been obtained.

Similar sections of an S colony show a regular edge and only short bacillary forms.

FROM AUTHORS' SUMMARY.

BACTERIOSTASIS. M. S. MARSHALL and A. K. HRENOFF, J. Infect. Dis. **61**:42, 1937.

A disinfectant spectrum has been used to picture the necessity for realization of the merging bands or ranges of concentrations of disinfectants through which these substances shift their activities from rapid germicidal action to barely perceptible inhibition.

The bacteriostatic ranges of 20 disinfectants acting on 6 types of organisms have been determined and charted for a given set of conditions. It is possible by the method used to measure a low degree of bacteriostasis but not necessarily the minimal degree.

The ranges of bacteriostasis determined are in no sense evaluations of the disinfectants studied, for reasons which are stated. The principle of relative evaluation of disinfectants is condemned. Equally condemned are the superficial and fundamentally erroneous and misleading brief laboratory answers to questions concerning disinfectants. The answers must come through basic and complete studies of single substances.

FROM AUTHORS' SUMMARY.

ENCAPSULATION OF HEMOLYTIC STREPTOCOCCI. G. L. HOBBY and M. H. DAWSON, Brit. J. Exper. Path. **18**:212, 1937.

A method is described by which capsules on hemolytic streptococci, groups A to F, can be demonstrated while the organisms are in the mucoid phase. Hemolytic streptococci of group A when isolated from disease conditions in man are usually encapsulated and in the mucoid phase.

FROM AUTHORS' SUMMARY.

FOWL PEST: THE SUSCEPTIBILITY OF MONKEYS, HEDGEHOGS AND OTHER ANIMALS. G. M. FINDLAY and R. D. MACKENZIE, Brit. J. Exper. Path. **18**:258, 1937.

Rhesus monkeys are susceptible to certain strains of the virus of fowl pest on intracerebral inoculation. They react with fever and generally with symptoms of ascending myelitis. At death virus is present in the brain, liver and spleen and in association with the formed elements of the blood but is not present in the blood serum. Rhesus monkeys inoculated intraperitoneally or intranasally do not

show any reaction but subsequently disclose that immune bodies have developed. Hedgehogs are susceptible to the virus of fowl pest when this is injected intracerebrally. Ducks are also susceptible on intracerebral but not on intramuscular injection. Pigeons may have nervous symptoms after intraperitoneal and intracerebral inoculation but die only when virus is inoculated by the latter route.

FROM AUTHORS' SUMMARY.

MICROSCOPIC CHANGES IN THE LUNGS OF MICE INFECTED WITH INFLUENZA VIRUS. M. STRAUB, J. Path. & Bact. **45**:75, 1937.

The primary lesion in experimental influenza of mice obtained with virus from man is necrobiosis and fibrinoid necrosis of the epithelium of the respiratory and terminal bronchioles, leading to a state of complete epithelial desquamation. Secondary to this epithelial process there occur dilatation of bronchioles and collapse of alveoli, with edema and hyperemia. Polymorphonuclear exudation is not a feature of the changes caused by the influenza virus. Widespread epithelial proliferation seems to be an early and essential part in the healing process. A state of chronic collapse of large parts of the lungs is produced and is easily demonstrable in roentgenograms. In surviving mice it is often found that only one pulmonary lobe is affected.

FROM AUTHOR'S SUMMARY.

IRRADIATION OF BACTERIOPHAGE WITH ULTRAVIOLET RAYS. M. L. CAMPBELL-RENTON, J. Path. & Bact. **45**:237, 1937.

Five races of bacteriophage were exposed to ultraviolet rays and compared as to their sensitivity to these rays, with the following results: Between the most and the least sensitive of the five races studied there is a difference of about six to eight times in the length of exposure required. The size of the plaques bears no obvious relation to the sensitivity of a bacteriophage to ultraviolet rays. Of two races of bacteriophage acting on the same culture of Bacillus paratyphosus B and having approximately the same size of plaque, one requires an exposure about five times longer than the other to destroy 60 per cent. In the two races most sensitive to ultraviolet rays a diffuse lysis, with or without plaques, was observed in longer exposures of undilated bacteriophage.

FROM AUTHOR'S SUMMARY.

DISEASES OF HOGS (BOUCHET'S DISEASE). PAUL DURAND, PAUL GIROUD, EDOUARD LARRIVÉ and ANDRÉ MESTRALLET, Arch. Inst. Pasteur de Tunis **26**:213 and 228, 1937.

The disease reported was observed in hogs in 1914. In 1932 the disease was reported by Müller, of Switzerland, to have been differentiated in human beings during the preceding five years. In animals the infection begins from fifteen to thirty days after exposures, with fever, vomiting and diarrhea. This is succeeded by a sharp drop in temperature, a typical exanthem and then meningeal symptoms. Direct transmission appeared not to occur, and some intermediate vector was suspected.

The use of the virus of this disease, which is relatively innocuous, with a remission period of forty-eight hours between febrile periods and accompanied by meningeal symptoms, in the treatment of patients for mental disease seemed reasonable. Therefore 78 patients were given the blood of an infected pig by injection, and 72 of them became infected. The period of incubation was about eight days (from four to seventeen), and the duration of illness ranged from three to twenty-one days. The febrile period did not invariably present a period of remission, but frequently it did; the eruptive stage was observed in 16 of the infected persons but was transient; it may have been overlooked in others; intestinal and meningeal symptoms appeared. The blood, spinal fluid and urine were shown to contain the virus. The virus was filtrable. Immunity appeared to follow an attack.

M. S. MARSHALL.

LYMPHOPHILIC VIRUS FROM SUBACUTE "MONOADENITIS." M. PETZETAKIS, Zentralbl. f. Bakt. (Abt. 1) **138**:32, 1936; **138**:137, 1937.

Petzetakis reports experiments in which extracts of tissues and of pus from lymph nodes of patients with subacute "monoadenitis" were injected intracutaneously into other patients ill with this disease and into patients with other diseases. In the former group, after thirty-six hours, marked inflammation occurred at the point of injection and persisted for from five to ten days. In contrast, when the same antigen was injected into 5 normal persons, into 3 patients with chronic tuberculosis of lymph nodes, into 5 with pulmonary tuberculosis and into 4 with malaria, the local reaction was completely negative.

Petzetakis injected the lymphophilic virus obtained from lymph nodes of patients with subacute "monoadenitis" intracerebrally into guinea pigs. After a short period of incubation symptoms of meningoencephalitis appeared, followed shortly by death of the animals. Histologic examination revealed lymphocytic infiltration of the meninges.

PAUL R. CANNON.

THE CAUSATIVE AGENT OF TYPHUS AND OF ROCKY MOUNTAIN FEVER. F. BREINL and E. CHROBOK, Zentralbl. f. Bakt. (Abt. 1) **138**:129, 1937.

Breinl and Chrobok found the cultivation of rickettsias of European typhus and of American Rocky Mountain spotted fever relatively easy in diluted serum containing pieces of guinea pig or rabbit organs. Tunica vaginalis proved to be the best tissue, although muscle tissue was also excellent. The rickettsias developed in later passages of both strains, those of the typhus strain appearing earlier than those of the Rocky Mountain spotted fever. Immune serums and immune organs had no influence on the development of the rickettsias, although in some instances there were evidences of agglutination in cultures grown in immune serum. Three photomicrographs illustrate the appearance of the rickettsias from these tissue cultures.

PAUL R. CANNON.

EXPERIMENTAL PNEUMONIA. B. BIELING and L. OELRICHS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **89**:312, 1936.

Pneumonia was produced in mice and guinea pigs by making them inhale bacteria in suspension. The animals which prior to inhalation were subjected to ether anesthesia acquired pneumonia more frequently than the animals anesthetized with an intravenously injected narcotic. This was due to differences in the numbers of inhaled bacteria brought about by more or less marked preservation of reflexes, as was demonstrated by inhalation experiments with india ink in suspension. The course of pulmonary lesions due to aspiration of colon bacilli and of those due to aspiration of diphtheria bacilli is described. A detailed study of the anatomic and bacteriologic findings in pneumococcic infections is presented, and the effects of serum therapy are discussed. The significance of the time factor is demonstrated by observing the relation between the administration of the immune serums, the infection, the extent of the anatomic involvement, the presence or absence of bacteremia and the outcome of the disease.

I. DAVIDSOHN.

Immunology

ALLERGY AND DESENSITIZATION IN TUBERCULOSIS. H. S. WILLIS and C. E. WOODRUFF, J. Clin. Investigation **16**:899, 1937.

Guinea pigs that have been allergic and have been desensitized experience a delay of several weeks in the development of tuberculosis after reinfection. This delay has been mistaken for retained immunity. Animals which have been prevented from becoming allergic by injection of tuberculin are unusually susceptible to tuberculosis and show what is probably the most marked degree of tuberculous

pneumonia yet produced in experimental animals. These observations indicate that it is unsafe as yet to conclude that the phenomena of allergy are an unessential part of the mechanism of defense against tuberculosis.

FROM AUTHORS' SUMMARY.

EFFECT OF INCREASED ANTIPNEUMOCOCCAL IMMUNITY ON THE INCEPTION OF EXPERIMENTAL LOBAR PNEUMONIA IN THE DOG. O. H. ROBERTSON, J. Exper. Med. **66**:705, 1937.

In view of the finding that one or more attacks of pneumococcic lobar pneumonia experimentally induced in dogs failed to protect the animals against subsequent infection, an attempt was made to determine whether or not antipneumococcus immunity in dogs could be enhanced to the degree of complete resistance. To this end dogs were passively immunized by injecting intravenously large quantities of both unconcentrated antipneumococcus horse serum and concentrated antibody solution and actively immunized by vaccination with killed and living cultures of pneumococci. None of these procedures resulted in constant protection against the pulmonary infection. The disease, however, was of brief duration, and the lesions were of limited extent and usually became sterile within twenty-four hours. A combination of active and passive immunization produced no better results. It was only when immune bodies and leukocytes were implanted with the infecting dose that infection was prevented with any degree of constancy. Even under these conditions the lesion sometimes involved a considerable portion of a lobe. The factors in the inception of experimental lobar pneumonia are discussed, and the bearing of this study on prophylactic immunization of human beings against pneumococcic pneumonia is suggested.

FROM AUTHOR'S SUMMARY.

PROTECTIVE INOCULATION WITH HEAT-KILLED TUBERCLE BACILLI. E. E. OPIE and J. FREUND, J. Exper. Med. **66**:761, 1937.

Repeated injections of heat-killed tubercle bacilli into or below the skin of rabbits increase conspicuously the resistance of the animals against infection with virulent tubercle bacilli. The protection against tuberculous infection is only slightly less than that given by BCG. Addition of certain antigens, notably heated horse serum, increases the protection given by heat-killed tubercle bacilli so that it is approximately the same as that afforded by BCG. These experiments and tentative observations on persons exposed to tuberculous infection indicate that heat-killed tubercle bacilli may be substituted for the living attenuated microorganisms in the attempt to increase resistance against tuberculous infection and to influence favorably the delicate balance between asymptomatic, or latent, infection and progressive, manifest disease.

FROM AUTHORS' SUMMARY.

ANTIGENIC DIFFERENCES IN MOUSE ERYTHROCYTES. P. A. GORER, Brit. J. Exper. Path. **18**:31, 1937.

With the aid of immune rabbit serum, Gorer succeeded in demonstrating a new antigenic difference between the red cells of three pure lines of mice, in addition to the three previously recorded. Tests for the new agglutinogen and one of those previously described on hybrids between two of the pure lines of mice gave results consistent with the hypothesis that the agglutinogens are determined by two independent, incompletely dominant autosomal genes.

A. S. WIENER.

INFLUENCE OF ROENTGEN RAYS ON THE PHAGOCYTIC PROPERTY OF GIANT CELLS. W. G. GARSCHIN, M. A. ZACHARJEWSKAJA and W. W. OSSINSKA JA, Frankfurt. Ztschr. f. Path. **49**:252, 1936.

The authors produced a giant cell granuloma by subcutaneous injection of cholesterol crystals in fine suspension. After twenty days the well developed

granuloma showed numerous giant cells containing cholesterol crystals, mononuclear xanthoma cells and ingrowing connective tissue. Two groups of experiments were performed, total roentgen dosages of 3 and 6 erythema units being used, which were distributed over twelve and twenty-four days, respectively, 0.5 unit being given at each exposure. The results were: (1) retardation of the invasion of connective tissue, (2) inhibition of the formation and proliferation of macrophages and (3) decrease in the lysis of cholesterol crystals. In general, the phagocytic activity of the granuloma cells was markedly decreased.

A. STRAUSS.

A HITHERTO UNKNOWN BLOOD GROUP A_3. V. FRIEDENREICH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **89**:409, 1936.

Among 4,000 blood specimens 6 extremely weak A bloods were found considerably less agglutinable than A_2. A study of 260 members of the families of the persons whose blood was in question revealed the presence of this very weak A—called by Friedenreich A_3—in 46 and of A_3B in 3. It is inherited in a manner similar to that of other factors but is dominated by the A_1 and A_2 factors just as A_2 is dominated by A^1. There is a danger that the presence of this factor may not be recognized unless strong typing serums are employed; three commercial typing serums failed to detect it. The serums of these persons did not have anti-A agglutinins of any kind. What effect the failure to recognize the A_3 factor in a donor might have on a recipient in case of a blood transfusion cannot be foreseen. According to Friedenreich, the failure to recognize A_3 would not lead to false conclusions in paternity tests, provided that the mode of inheritance is as postulated by him.

I. DAVIDSOHN.

THE DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF THE MEINICKE TEST FOR TUBERCULOSIS. E. PIECK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **90**:358, 1937.

The Meinicke test for tuberculosis employs the antigenic extract of Klopstock, Witebsky, Kahn and Klingenstein and is known as the Meinicke immune ball test. Pieck used it in 100 cases of tuberculosis, clinically established. Of 433 cases of active tuberculosis, it was positive in 76.2 per cent, doubtful in 13.6 per cent and negative in 10.2 per cent. Some of the negative and doubtful results were obtained in cases in which the disease was advanced, with many cavities, in cases in which a latent process recently had become active or in cases in which the disease was in an early stage. Of 134 cases of arrested tuberculosis, the test was positive in 19.4 per cent, doubtful in 34.3 per cent and negative in 46.3 per cent. According to Pieck, no prognostic significance attaches to the results of the test. Of 108 clinically nontuberculous persons 85.2 per cent gave negative, 7.4 per cent doubtful and 7.4 per cent positive reactions. The last had histories suggestive of positive findings in the past.

I. DAVIDSOHN.

DEMONSTRATION OF THE ANTIGEN OF CASEOUS MATTER IN GROSSLY UNCHANGED ORGANS. L. DMOCHOWSKI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **90**:363, 1937.

Hirszfeld and Halber demonstrated cancerous antigenic substances in the grossly uninvolved liver of a patient with carcinoma of the stomach. They labeled this phenomenon "a biochemical metastasis." They and others also demonstrated the serologic specificity of necrotic cheesy and purulent material, as distinct from organ specificity. Dmochowski investigated the possibility of the presence of antigenic substances of the same nature as caseous matter or pus in grossly uninvolved organs of patients with tuberculosis and chronic suppurations. A specific immune serum was produced by inoculating rabbits with cheesy material

from tuberculous pulmonary lesions of cattle. Raw and boiled aqueous extracts of grossly unchanged organs did not react in the complement fixation test, while alcoholic and ethereal extracts of such organs of patients with tuberculosis and with chronic suppurations reacted in complement fixation and precipitation tests with the immune serum, while similar extracts of organs of patients dying from other causes did not react except for an occasional reaction of splenic extracts. Sputum of tuberculous patients reacted in the form of raw and boiled aqueous extracts as well as in alcoholic extracts. Lecithin added to the extracts tended to strengthen the specific and weaken the nonspecific reactions.

I. DAVIDSOHN.

Tumors

SARCOMA IN RATS FROM THE INGESTION OF A CRUDE OIL OBTAINED BY ETHER EXTRACTION OF WHEAT GERM. L. G. ROWNTREE and others, Am. J. Cancer **31**:359, 1937.

Neoplasms have been produced in 70 rats of the Wistar strain through the oral administration of a crude oil prepared by ether extraction of wheat germ. These tumors developed in the abdominal cavity, were malignant and were readily transplantable. On microscopic examination they proved to be spindle cell sarcoma. Tumors identical in nature have been produced in two other strains of rats—Buffalo and Yale albino. The nature of the sarcogenic agent has not as yet been determined. It is not known whether it is inherent in the germ or is produced in the process of extraction.

FROM AUTHORS' SUMMARY.

PAGET'S DISEASE OF THE SKIN AND ITS RELATION TO CARCINOMA OF THE APOCRINE SWEAT GLANDS. H. W. WEINER, Am. J. Cancer **31**:373, 1937.

Paget's disease, both mammary and extramammary, was first described in 1874, but its nature is still disputed. An instance of the disease occurring in the vulva is reported with the observations at necropsy. From 57 extramammary cases recorded in the literature, no necropsy report is available, and only 15 are reported in sufficient detail to warrant a definite diagnosis. An additional 10 are probably cases of Paget's disease. The present case is strongly corroborative of the view of Jacobaeus, Muir and others as to the nature of the disease. It is their belief that the lesion of the skin is the result of intraepidermal metastases from an underlying cancer. That is, the Paget cell is a cancer cell. In all of the acceptable extramammary cases the lesion was located either in the axilla or in the anogenital region, sites in which the sweat glands are of the apocrine variety. The mammary glands are also modified sweat glands. It is suggested that Paget's disease of the skin is an intraepidermal metastasis from an underlying carcinoma of the apocrine sweat glands. It is noteworthy that in the reported extramammary cases the carcinoma, whenever characterized, is described as glandular in type.

FROM AUTHOR'S SUMMARY.

NONFILTRABLE FOWL TUMORS. L. FOULDS, Am. J. Cancer **31**:404, 1937.

Noninfective extracts of a tumor induced by 1,2,5,6-dibenzanthracene were injected into rabbits, which then yielded serum which neutralized filtrates of Rous sarcoma 1. Reasons are given for deducing that a virus was present in the nonfiltrable tumor. The significance of the nonfiltrable tumor is discussed in detail. It is concluded that in virus tumors an intracellular virus-protoplasm complex is formed, and filtrability depends on dissociation of this complex in a particular way. This conception seems essential to an understanding of the cellular pathology of virus tumors.

FROM AUTHOR'S SUMMARY.

PRODUCTION OF TUMORS BY CULTURES OF NORMAL CELLS TREATED WITH FILTRATES OF FILTRABLE FOWL TUMORS. R. J. LUDFORD, Am. J. Cancer **31**:414, 1937.

The results indicate that fibroblasts and not macrophages are the cells which are sensitive to "infection" with the viruses of the Fujinami and the Rous sarcoma and that the malignant cells of these neoplasms are transformed fibroblasts.

CYTOTOXINS LETHAL TO NUCLEATED MAMMALIAN CELLS, NORMAL AND MALIGNANT. T. LUMSDEN, Am. J. Cancer **31**:430, 1937.

Whether there are antibodies specifically toxic for each particular type of tissue or cell used as antigen is still not demonstrated, but there is some indication that cancer cells contain a constituent capable of working cytotoxins (anticancer bodies) lethal to malignant cells and not to normal cells. Their absolute specificity is masked, however, by the heterotoxins or homotoxins which accompany them.

FROM AUTHOR'S SUMMARY.

A NOTE ON THE NONSPECIFIC ACTION OF SO-CALLED "ANTICANCER SERUM." H. J. PHELPS, Am. J. Cancer **31**:441, 1937.

The observations recorded in this note show that an antiserum for Jensen rat sarcoma kills both the sarcoma cells and the normal spleen cells; and that an antiserum for spleen kills both normal spleen and sarcoma cells. The conclusions drawn from the facts elicited are (1) that "anticancer serum" has no specific action on malignant cells, (2) that the antigen in cancer cells which gives rise to the antibodies studied is not peculiar to malignant cells, (3) that the antibodies are probably isoantibodies formed in response to injections of foreign though homologous cells and (4) that the antiserums, from their nature, probably cannot be therapeutically useful.

FROM AUTHOR'S SUMMARY.

MENINGIOMA. J. H. GLOBUS, Arch. Neurol. & Psychiat. **38**:667, 1937.

Basing his observations on a study of 103 specimens obtained at necropsy and after operation and applying the principles of otogenesis and phylogenesis, Globus concludes that six main types of meningioma can be recognized: (1) meningioma undifferentiale, or mesenchymatous meningioma, which in its structure resembles undifferentiated meningeal primordium; (2) meningioma omniforme, in which the elements in some parts of the tumor are more differentiated than those in the previous form, though grossly both may be alike; (3) pachymeningioma, or dural fibroblastoma, in which collagen fibers predominate and the dura alone is represented—a very rare tumor; (4) leptomeningioma, or arachnoid meningioma, which consists of cell groups arranged as cords or whorls and which may invade the dura and brain and contain elements of each; (5) meningioma piale, or vascular meningioma, which contains only pial components—capillaries, sinusoids and "foam" cells; with this group, as subtypes, are included psammomas and melanoblastomas. In some tumors, the cellular elements may undergo sarcomatous changes; hence there occurs (6) sarcomatous meningioma, which may be diffuse (meningeal) or circumscribed (cerebral).

GEORGE B. HASSIN.

PRIMARY BRONCHOGENIC CARCINOMA. W. L. MATTICK and E. M. BURKE, J. A. M. A. **109**:2121, 1937.

In 65 of 73 cases of bronchial carcinoma the nature of the condition was established by histologic examination of a section obtained at biopsy or at autopsy.

Although histologic study in 62 cases showed a general pleomorphism, there was also a predominance of certain histologic architectural trends, depending on the degree of cellular differentiation.

No correlation between age of occurrence, anatomic location of the primary lesion, radiosensitivity, degree of malignancy, survival and the histologic groups could be demonstrated.

The most common roentgen characteristics were atelectasis in the central (i. e., hilar) type and tumor in the peripheral type, which was found in only 11 per cent of the cases in this series.

The predominance of a central location of the primary lesion, the tendency to early and distant metastasis and the marked pleomorphic picture conspire to make the prognosis unsatisfactory whether treatment is by surgical intervention or by irradiation. FROM AUTHORS' SUMMARY.

PHEOCHROMOCYTOMA AND HYPERTENSION. D. G. F. EDWARD, J. Path. & Bact. **45**: 391, 1937.

A case of pheochromocytoma associated with hypertension is described. The total epinephrine content of the tumor as estimated by Folin's method was 81.3 mg. and as estimated physiologically on the atropinized spinal cat 73.5 mg. Fifty-five other cases have been previously described, and the reports are summarized in the appendix. It is noted that tumors of this type have been confused histologically with cortical tumors; it is shown that they may contain fat and lipoid but that this fact does not necessarily indicate a cortical origin. It is stressed that pheochromocytoma may be associated with constant as well as with paroxysmal hypertension. So far as conclusions may be drawn from the few reported cases (7), the epinephrine content of the pheochromocytoma does not appear to be in proportion to the degree of hypertension. FROM AUTHOR'S SUMMARY.

HYPERPLASIA OF BONE MARROW ASSOCIATED WITH DISSEMINATION OF CANCER. J. W. ORR, J. Path. & Bact. **45**:579, 1937.

The bone marrow of rats, mice, rabbits and guinea pigs bearing malignant tumors was studied. The marrow was hyperplastic in all rabbits and guinea pigs with metastases and in some of those with large primary growths only. In rats and mice hyperplasia of the marrow was less convincing because of the greater normal cellularity of the marrow in these animals, but there was adequate evidence that it occurred in these animals also. The hyperplasia involved the leukopoietic or the erythropoietic tissue or both, but most frequently the leukopoietic element predominated, especially when the tumor process was advanced. The erythropoietic cells still showed great regenerative activity when the spread of the neoplasm was associated with hemorrhage. In mice, rapidly growing tumors—which are also those with the most necrosis—give rise to the most hyperplasia of the marrow. FROM AUTHOR'S SUMMARY.

A SEROLOGIC TEST FOR CANCER. M. ARON, Presse méd. **45**:1403, 1937.

Aron reported in previous papers (*Presse méd.* **42**:833, 1934; **43**:1044, 1935) the finding of an alcohol-insoluble specific substance in the urine of patients with cancer. Rabbits given injections of the precipitate showed characteristic changes in the adrenal glands. When the serum of rabbits and sheep that had received repeated injections of the cancer specific substance was injected into other rabbits, it protected them against the action of the cancer specific substance; i. e., lesions did not develop in their adrenals. Aron assumed that there was a specific antigenic substance in the urine of cancerous patients. He found that properly prepared antigen produced a characteristic flocculation with the serum of patients who had cancer but not with the serum of patients who were free from cancer. He gives detailed directions for the preparation of the antigen: The urine is obtained from patients with advanced cancer but free from other diseases. It is advisable to select urine free from albumin. Three volumes of 95 per cent alcohol are added to one volume of urine; the precipitate is dried in vacuum. A method is given for the removal of the phosphates. The precipitate is dissolved, the p_H is adjusted to 6.8, a part of the solution is heated to 70 C., and another part is heated

to 90 C., to be used as a negative control. Another technic permits the preparation of a concentrated antigen. For the test 2 cc. of the antigenic solution is mixed with each of a few graded quantities of the serum. The mixture of the antigen heated at 90 C. with the serum serves as control, which must remain perfectly clear. The test is read after varying intervals, the final reading being after forty hours. In cases of cancer a precipitate develops. In cases in which there is no cancer the serum-antigen mixture remains perfectly clear; or, if it shows a precipitate, a precipitate of varying intensity is also present in the control. Aron explains the latter phenomenon by the presence in the urine of antigenic substances that are specific not only for cancer but also for various other diseases. Aron has had excellent results with his test, but he has also had failures in the form of false positive reactions. He does not think that the test is ready for general use.

I. DAVIDSOHN.

THE HYPOPHYSIS AND EXPERIMENTAL CANCER. F. SAUERBRUCH and E. KNAKE, Arch. f. klin. Chir. **189**:185, 1937.

This article is the follow-up of a preliminary report (Sauerbruch, F., and Knake, E.: *Ztschr. f. Krebsforsch.* **44**:223, 1936). The investigation was suggested by the well known clinical observation of disturbed sexual functions in many young persons with malignant tumors. Sauerbruch and Knake assumed that the disturbances of the sexual functions create conditions favorable for the formation of tumors. They did not use any known carcinogenic agents but relatively slight injuries, for instance, small wounds or injections of lactic acid or of cholesterol. Rats were castrated or their sexual function weakened by parabiotic union. Eight malignant tumors and among them five with metastases were produced in 60 rats while only one tumor developed in 40 control (not castrated) animals. Sauerbruch and Knake explain their results by the increased growth-promoting action of the hormones of the anterior lobe of the pituitary. Normally, the hormones of the pituitary find an outlet through their action on the ovary; when the latter fails to function the growth-promoting factors of the pituitary favor tumor formation. Splenectomy is followed by increased elimination of pituitary substances. The action of the spleen may be either inhibitory to the formation of the hormone or destructive of the product. Senile atrophy of the spleen creates indirectly favorable conditions for the formation of tumors by the elimination of the spleen's interfering influence on the pituitary hormones. Resistance to the formation of tumors depends on undisturbed function of the gonads, spleen and hypophysis.

I. DAVIDSOHN.

TISSUE REACTIONS AROUND TUMOR IMPLANTS IN MAN. W. UHER, Ztschr. f. Krebsforsch. **45**:74, 1936.

Incidental to experiments conducted for another purpose, Uher had an opportunity to study the tissue changes which resulted after implantation of human cancerous tissue in man; for this purpose persons who were apparently moribund were selected, although some were alive several months later. The tumor tissues were from mammary cancers and one malignant melanoma. Successful implantation was never observed. There was a prompt acute inflammatory reaction, with rapid appearance of degenerative changes in the cancer cells. There followed gradual infiltration by histiocytes and fibroblastic overgrowth, with the appearance later of lymphocytes and giant cells. In those persons who survived for several months, the previous presence of tumor tissue was indicated only by some persistent connective tissue overgrowth and, in the case of the melanotic tumor, pigmented débris, partly phagocytosed. Controls inoculated with normal liver cells gave similar results, but here disintegration was faster and more uniform.

H. E. EGGERS.

THE CAMPAIGN AGAINST CANCER. M. MEYER, Ztschr. f. Krebsforsch. **45**:91, 1936.

Meyer discusses the collection of statistical material concerning morbidity from cancer and illustrates by means of three sets of questionnaires, representing as many attempts at collection of such material by German authorities. These questionnaires, incidentally, reflect interestingly the alterations in the views about the causes of cancers which have come with increasing knowledge of the subject. In order to get data of sufficiently comprehensive character, Meyer urges collection of such data through the cooperation of organized medicine; but their elaboration, in his opinion, is a matter for trained statisticians, best working under governmental auspices.

H. E. EGGERS.

Technical

STUDIES ON THE KLINE TEST FOR SYPHILIS: I. QUANTITATIVE ASPECTS. A. S. WIENER, J. Lab. & Clin. Med. **22**:1062, 1937.

The following technic is described for performing the quantitative Kline test: To each of a series of small tubes the same number of drops (usually 5) of physiologic solution of sodium chloride is added. One drop (0.05 cc.) of the undiluted inactivated serum is placed in the first well of a paraffin ring slide and then 5 drops of serum is placed in the first tube of the series. After thorough mixing 1 drop of the 1:2 dilution of serum is placed in the second well of the slide and 5 drops of the diluted serum is transferred to the second tube of the series. By mixing the saline solution and the 1:2 dilution of serum a 1:4 dilution is prepared, and the process is repeated, the dilutions being carried out as far as desired. Then 1 drop (0.008 cc.) of antigen is added to each well, the slide is rotated rapidly for four minutes, and the reactions read. The reciprocal of the highest dilution which gives a distinct reaction equals the number of units of reagin present in the serum. By this method it can be shown that the "Kline exclusion" antigen is approximately twice as sensitive as the "Kline diagnostic" antigen.

Certain advantages of the Kline test are pointed out. The test is equal or superior in both sensitivity and specificity to the better Wassermann and flocculation tests in use today. The process is easy to standardize and maintain at a constant level of sensitivity. Thus, in parallel tests performed on a series of more than 600 blood specimens, Wiener, Kline and Rein obtained almost entirely identical results, despite the fact that the tests were performed under entirely different laboratory conditions and with entirely different reagents. Another advantage of the test is the remarkable stability of the emulsions of antigen, so that the emulsions can be used as stock reagents, particularly for tests on blood donors before transfusions. Finally, with the Kline test one can obtain optimal results as far as specificity and sensitivity are concerned, with the expenditure of a mimimal amount of effort, time and money for reagents and equipment.

A. S. WIENER.

USE OF CONCENTRATED SERUM AND OTHER METHODS OF DEMONSTRATING WEAK N RECEPTORS IN HUMAN BLOOD. F. PIETRUSKY, Deutsche Ztschr. f. d. ges. gerichtl. Med. **28**:468, 1937.

Pietrusky describes a method of preparing concentrated pure anti-N fluid. The unabsorbed immune serum is diluted one hundred times with physiologic solution of sodium chloride and absorbed with one and one-quarter times its volume of washed, packed AM cells. The absorbed diluted serum is then concentrated to one tenth of its volume and is then rendered isotonic by dialyzing it for twelve hours. If the concentrated serum is then found to give a reaction with blood not containing property N, it is reabsorbed with small additional amounts of AM blood. According to Pietrusky, such fluid agglutinates weak N, or so-called N_2, blood within five minutes, whereas tests set up with M blood are still negative after twenty minutes. The same method of concentrating serum may be applied

to obtain high-titered anti-A_1 serum, and it is claimed that by applying this method to the preparation of anti-M serum a pure anti-M serum was obtained which reacted in a dilution of 1 : 2,000. Since this method of concentrating anti-N serum is laborious and expensive, Pietrusky describes simpler methods, which are also satisfactory for N_2 blood, and in which ordinary potent anti-N testing fluids may be used. For example, the tests can be set up on glass slides in an ice box at 5 C., and observed and compared with similar tests on pure M blood. Or the tests can be done by the centrifuge method, with use of test tubes which have been previously cooled in the ice box.

A. S. WIENER.

THE KEEPING QUALITIES OF ABSORBED M AND N IMMUNE SERUMS. S. OLBRICH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **90**:271, 1937.

As described in a previously published report, Olbrich developed a procedure for accurate absorption of M and N serum. He kept absorbed specimens over long periods and checked them at six month intervals. Few kept the same titers longer than two years, but if proper precautions were observed it was easy to obtain absorbed specimens which kept the same titers for at least six months. Olbrich recommends that preservatives should not be used. Aseptic precautions are essential, but he noticed that even if bacteria grew in absorbed serum the titer was not affected. Dried absorbed serum proved equally satisfactory but not superior. After a consideration of all factors the individuality of an immune serum determines primarily the keeping qualities of the absorbed specimens. Olbrich advocates supervision and certification by the government of serum used for medicolegal purposes.

I. DAVIDSOHN.

Society Transactions

NEW ENGLAND PATHOLOGICAL SOCIETY

FREDERIC PARKER JR., BOSTON, *President*

Jan. 20, 1938

J. B. HAZARD, BOSTON, *Secretary*

MORPHOLOGIC AND PHYSIOLOGIC OBSERVATIONS ON REFRACTORY ANEMIA. C. P. RHOADS (by invitation), New York.

One hundred cases of anemia of a type refractory to accepted methods of treatment have been studied at the hospital of Rockefeller Institute for Medical Research, New York, over a period of five years. Histologic studies of both biopsy and autopsy specimens of sternal marrow showed several pathologic subdivisions, which are characterized, respectively, by (1) predominance of young, undifferentiated marrow cells, (2) total hypoplasia and (3) hyperplasia. Studies of the excretion of pigment gave evidence of a hemolytic process. A fourth group was marked by sclerosis of the marrow structure. Clinical studies showed that transitions from one type to another may occur during the course of the disease in certain instances. Moreover, in spite of the bad prognosis ordinarily given in this type of case, temporary remissions are common, and sustained remissions have been encountered.

In 30 per cent of the entire group of cases the condition was secondary either to a malignant process or to hepatic disease. Of the 70 primary cases, 35 (50 per cent) were associated with a distinct history of exposure to a variety of potentially toxic aromatic compounds, and the coincidence of exposure and symptoms was striking. The demonstration of a direct toxic effect of aminopyrine on the hemopoietic system suggested that some similar, but perhaps not identical, mechanism might exist in refractory anemia. Accordingly, a hemopoietically toxic substance was searched for in the blood and urine of the patients. Such a substance has been reported to occur in the urine of normal persons. In the urine of the patients with refractory anemia it was found in a bound or conjugated form. A similar substance was demonstrated in the blood of normal persons and, in increased amounts, in that of the patients with refractory anemia. Its nature is sterolic, but it has not been completely identified. A natural inhibitor of the substance has been isolated.

Since the amounts of toxic substance to which the patients had been exposed were slight, an experimental method of increasing the susceptibility of the hemopoietic system to such compounds was required. It was found that certain forms of deficiency disease conditioned the toxic effect of both exogenous and endogenous aromatic compounds. Clinical studies of patients with refractory anemia showed a metabolism of aromatic substances which differed from that of the normal.

A spectroscopic technic was developed by which the metabolism of certain endogenous and exogenous cyclic compounds might be followed. Applications of this technic to cases of refractory anemia showed distinct variation from normal, and in certain instances the abnormality seemed to concern estrogen or some allied substance. Administration of large amounts of estrogen to dogs resulted in a picture clinically, pathologically and spectroscopically indistinguishable from that in certain types of refractory anemia in man.

The suggestion is advanced that refractory anemia in man may be related to an abnormal production or metabolism of an endogenous cyclic hydrocarbon or to exposure to or an abnormal metabolism of such a substance from an exogenous source.

DISCUSSION

WILLIAM DAMESHEK, Boston: Dr. Rhoads' paper shows both imaginative and intelligent work in hematology. I have also been interested in these cases of refractory anemia and have often stressed the importance of doing biopsies of the bone marrow in them. I think every one has agreed that the diagnosis is difficult, sometimes even after biopsy. The marrow sections are frequently puzzling. Sometimes they do not give the entire picture, and there is often great difficulty of interpretation. They may show shrinkage, but smears of the marrow made at the time of biopsy offer considerable help in the identification of cells.

I am not clear as to what Dr. Rhoads considers "primitive cells." Whether a certain primitive cell belongs to the white or to the erythrocytic series is sometimes puzzling. My associates and I think, however, that we can distinguish the primitive red from the primitive white blood cells in most cases and have assigned to them the name "erythrogones." This term is used to designate the primitive cells that are increased in pernicious anemia and in hyperplastic marrow of all types. We have not seen hyperplastic marrow of this type in aplastic anemia. However, this might be due to a difference in interpretation rather than to absence of this type of marrow.

We have looked for exposure to chemicals in all cases of leukemia with a view of the possibility of getting a suggestive lead. Recently a series of patients gave such a history, and I feel that this cannot be entirely ignored. A careful history is necessary to reveal such a relationship, for it may be so indirect as to be readily missed.

The problem of the lysins is interesting, and it is one we have been working on recently. I think there is no question that the presence of lytic substances will prove to be an important lead in some of these cases of refractory anemia.

J. B. HAZARD, Boston: I should like to ask Dr. Rhoads whether in the cases of osteosclerosis mentioned any history of exposure to silica was elicited.

C. P. RHOADS, New York (by invitation): In reply to Dr. Dameshek, may I say that my associates and I have not been able to identify positively the primitive cells. All studies of marrow have been controlled by smears stained supravitally and by Wright's stain.

I failed to call attention to Dr. Dameshek's recent paper on lysins. This has opened up a new field in the blood dyscrasias.

Our 3 patients with osteosclerotic anemia gave no history of exposure to silicates. There is still much to be learned as to the etiology of osteosclerotic anemia. One patient has had a complete remission.

W. B. CASTLE, Boston: Dr. Rhoads has presented a logical and frontier-seeking paper. Would it be possible to establish whether the primitive cells are susceptible to lysis by saponin by setting up a suspension of marrow and adding the agent directly to it?

C. P. RHOADS, New York (by invitation): We have had this experiment in mind.

VALY MENKIN, Boston: Is there any relation between the substances you have demonstrated in the blood and the carcinogenic compounds?

C. P. RHOADS, New York (by invitation): The compounds have not been positively identified, so it is impossible to say.

WILLIAM DAMESHEK, Boston: Why are the erythrocytes so large in pernicious anemia?

C. P. RHOADS, New York (by invitation): I do not know why this is so. Dr. Ponder has shown that the red blood cells in pernicious anemia are not susceptible to lysis with saponin. A structural change is inferred.

NEW YORK PATHOLOGICAL SOCIETY

ALFRED PLAUT, *President*

Regular Monthly Meeting, April 28, 1938

ROBERT A. MOORE, *Secretary*

PRIMARY CARCINOMA OF THE NAIL. JAMES R. LISA and JACOB LEVINE.

The patient was a 65 year old white man whose chief complaint was pain in the left great toe. The appearance of the toe suggested an ingrowing nail, but the toe failed to heal when so treated. Amputation was performed later. Pathologic examination revealed squamous cell carcinoma originating from the nail bed. Seventeen other cases were found reported in the literature. Trauma followed by chronic infection preceded the malignant change in many cases. The sites of predilection were the index finger and the thumb of the right hand and the great and little toes. The malignancy seems to be of low grade.

This paper is to be published in full in the *Archives of Surgery*.

DISCUSSION

ALFRED PLAUT: May I ask what the prognosis is in these cases?

JAMES R. LISA: It is excellent. Only once have metastases been observed, and in that instance the lesion had been present a year and a half. There were metastases to the inguinal lymph nodes, and the patient died following amputation, but in the series of 18 cases which we were able to find record of this was the only one in which there were metastases. There were a few cases in which there was local recurrence; in most of these the lesion had been treated by radium. In practically all the cases, however, either removal of the nail or amputation resulted in cure.

ALFRED PLAUT: Is calcification mentioned in any of the reports of cases?

JAMES R. LISA: None in the tumor itself. There were 2 or 3 instances in which the bone was invaded locally. Most of the reports of cases made no mention of bone involvement or mentioned simply erosion.

A. M. SALA: This patient has been followed at the New York City Cancer Institute Hospital. No sign of recurrence or of metastasis has been witnessed so far.

TUBEROUS SCLEROSIS WITH CEREBELLAR INVOLVEMENT AND A COLLOID CYST OF THE SEPTUM PELLUCIDUM. AMOUR F. LIBER.

In tuberous sclerosis, the cerebellum is rarely involved. Only 7 cases could be found by a review of the literature. The present case concerns a 16 year old girl who presented the characteristic clinical triad of tuberous sclerosis: mental deficiency, epilepsy and adenoma sebaceum of the face. She died with signs of intracranial hypertension. The autopsy showed multiple bilateral lipofibroleiomyoma of the kidney. The cerebrum showed typical lesions of tuberous sclerosis in both hemispheres. There were multiple subependymal nodules with calcific deposits about the lateral ventricles. From one of these nodules in the frontal horn a large intraventricular astrocytoma grew. The cavum septi pellucidi was filled with gelatinous material and was dilated to such an extent that it almost filled both frontal horns. The cerebellum presented a small whitish depressed hard area. In the subjacent white matter were multiple grossly visible calcific nodules. Microscopically, this lesion was notably different from those in the cerebral cortex. The affected cerebellar folia were transformed into masses of dense anisotropic scarlike fibrillar gliosis. In the middle of the patch, ganglion cells were absent. They reappeared gradually toward the periphery. There were no monstrous or aberrant cells. In the molecular layer were numerous and typical heme bodies.

The gelatinous material in the cavum septi pellucidi may be interpreted either as a congenital anomaly, analogous to colloid cyst of the third ventricle, or else as a consequence of transudation from the astrocytoma which adhered to one leaf of the septum. The finding of heme bodies in tuberous sclerosis shows that cavitation is not an essential factor for the presence of these structures. Gliosis and compression were present in this case, as in all previously known cases of heme bodies.

A Consideration of Certain Types of Benign Tumors of the Placenta. Andrew A. Marchetti (by invitation).

The benign tumor of the placenta designated as chorioangioma is relatively rare. In a careful review of the literature it was possible to bring the total number of reported cases to 209. The addition here of 8 instances produces a new total of 217 reported cases of chorioangioma. In the Lying-in Hospital, New York, an incidence of approximately 1 chorioangioma in 3,500 placentas was found.

On the basis of their histologic structure they are differentiated into various types. The cellular or immature type, the vascular or more mature type and that accompanied by varying degrees of degenerative changes are representative.

The histogenesis of these tumors is fairly well established. The tissue originates from the chorionic mesenchyme, the proliferating endothelium and blood vessels playing the leading role, the stroma an accessory role.

Whether a chorioangioma is a true tumor, according to Ribbert's idea, or a malformation, as explained by R. Meyer, remains an open question.

With the possible exception of hydramnios and of the extremely rare possibility of dystocia, it may be concluded from the evidence at hand that chorioangioma is clinically insignificant.

DISCUSSION

Alfred Plaut: I am grateful to Dr. Marchetti that he has presented something about these rare and often misinterpreted lesions. Probably he agrees with me that placental tumors, like other placental lesions, occur often when one examines placentas oneself and are extremely rare when one delegates the regular so-called inspection of placentas to somebody else. As was obvious from Dr. Marchetti's photographs, such a lesion is not easily recognized from the outside. The same applies to the microscopic appearance, as was apparent from the lantern slides. I also agree with Dr. Marchetti that the old discussion whether such a lesion is a true tumor or a hamartoma or a hamartoblastoma is more interesting from the philologic standpoint than from that of pathologic anatomy.

The Passage of Substances Through Tissues and the Formation of Lymph. Robert J. Parsons (by invitation) and Philip D. McMaster (by invitation).

A vital dye, pontamine sky blue, has been introduced in minute amounts into the interstitial tissues or into the lymphatics of the ears of mice and rabbits and the movement of the dye in the tissues or through the channels has been observed under various physiologic conditions. The results suggest that in normal tissue dye moves first along or between connective tissue fibers and later diffuses away from them. Any manipulation of the ear speeds the movement of the dye through the tissues or through the lymphatics.

Experiments have been devised to study the effect of the pulse on the movement of dye in the tissues and on the formation and flow of lymph. Amputated rabbit's ears were perfused with defibrinated, warmed and aerated rabbit's blood at constant pressure (141 mm. of mercury) and at pulsatile pressures (systolic 141 mm. and diastolic of 60 mm. of mercury). Lymph formation and lymph flow were from fifteen to twenty times greater and dye spread more rapid when the pulsating current of blood was used.

CHICAGO PATHOLOGICAL SOCIETY

FRANCIS D. GUNN, *President*

Regular Monthly Meeting, May 9, 1938

EDWIN F. HIRSCH, *Secretary*

OCCURRENCE OF GIANT CELLS IN CYSTITIS. H. G. WELLS.

This article appeared in full in the July issue of the ARCHIVES, page 32.

FURTHER STUDIES ON THE EVOLUTION OF THE PRIMARY TUBERCLE. HENRY C. SWEANY.

I have examined primary tubercles from 100 patients having accurate histories of contact with the disease, 27 of whom were infected before the age of 5 years and 73 later. There is an interesting parallelism between the age of the tubercles and the morphologic changes. The changes observed may be summarized as follows: A nebulous mass of inflammatory cells appears in the tissue structures during the first few weeks. These are largely polymorphonuclear leukocytes, monocytes, lymphocytes and fibroblasts, with varying amounts of inflammatory exudate as the age advances. They are mixed to a certain extent and overlap each other. Early there are central coagulation necrosis and subsequent caseation. Gradually connective and reticular tissues around the outside form a nonspecific wall. Much of this is apparently a mechanical crowding of the peripheral tissue by the region with inflammation. After this nonspecific wall has formed during the first few months, there is an increase of monocytes between these fibers and the caseous center. The change from monocytes to epithelioid cells and then to fibroblasts, according to K. E. Ranke (Ausgewählte Schriften zur Tuberkulose-pathologie, Berlin, Julius Springer, 1928, vol. 6, p. 67), is a metaplasia. These have no regular arrangement and increase for about a year with gradual transition to fibroblasts. Perhaps the native reticulum proliferates into fibroblasts. The inner fibroblastic layer, forming within six months, becomes connective tissue, clearly visible as a capsule at two years. This is part, if not all, of the so-called specific capsule of Aschoff. The capsule thickens for about three years; then calcification from within begins and replaces it by the fifth year. Simultaneously an outer layer of nonspecific fibers and native reticulum form a wall around the so-called inner capsule. This layer designated middle gradually thickens for seven or eight years, when it reaches its maximum. By this time it is dense and hyaline. Preceding this, usually caseation and calcification have converted the central core into a calcified mass. Calcification begins focally in the center and progresses toward the periphery as a thin ring. It is visible first in the postmortem roentgenogram when the tubercle has been present for about one year, becomes sharp after two years and appears as a broad band by four years. The central opening closes after from six to seven years. Not all lesions have the same density of calcification, and primary lesions in adults progress more slowly than those in infants and children.

At about five years, the old fibrocytes adjacent to the calcification undergo a form of metaplasia into peculiar phagocytic cells. The cells seem to grow at the expense of the calcified center on the inside and the old fibrous tissue on the outside, leaving lacunae of various sizes. Morphologically, the cells vary. Some are small, with densely stained nuclei and acidophilic cytoplasm, while others are large and resemble histiocytes of the fixed tissues. Still others seem to be ordinary fibroblasts originating from the basic reticulum. During this evolution of tissue, capillaries from adjacent vessels develop, although large lacunae may form without their presence. When the capillaries appear, the cells within assume greater activity and erode large openings into the calcified portions. These cells resemble fibroblasts and seem to follow the reticulum in the core of the tubercle.

The reticulum seems to serve as the framework on which the fibroblasts develop if it is not actually a precursor of the fibroblasts. The capillaries ramify and spread into the lacunae (*Am. Rev. Tuberc.* **37**:484, 1938).

After about ten years, the fibroblasts lining the lacunae or occasionally present around the outer wall are fibrillar and become collagenous and dense. The nuclei are angular, often pentagonal; the cytoplasm is solid and resembles bone. As years pass, the lacunae become larger, until after twenty years, when approximately one third of the region has been resorbed. In the late stages, bone sometimes forms directly from fibrocytes, laid down in thin layers and ossified. Sometimes the cells in the lamellae resemble osteocytes without metaplasia. The inner margins of the bone may be resorbed by cells similar to those causing the original erosions, but never have true osteoclasts been found.

Coincident with the formation of bone is the formation of the elements of bone marrow. Yellow marrow is usual, red marrow occasional. Blood vessels, reticulum, connective tissue and hemopoietic elements form in varying amounts. Most of the marrow tissue is primitive. Occasionally lymphoid tissues develop in lymph node tubercles, instead of marrow. This suggests that a histologic accommodation exists in the entire process.

Almost every tubercle that has been present over twenty years contains bone, the quantity of which is roughly proportional to the time elapsed in formation. These evolutionary changes may seem phenomenal, because a tubercle differs markedly from intramembranous bone. However, all changes are in the connective or basic reticulum tissues, and the morphologic appearances are not considered to be the inherent nature and function of the cells. While most of the changes may be classed as true metaplasia, all seem to be an adjustment to the environment. They illustrate the marked plasticity of the reticulum and connective tissues of the body.

Other interesting structures in tubercles that have been present up to thirteen years are the giant cells lying between the capsule and the core. These are numerous in tubercles up to a year, common up to four years and decrease up to thirteen years. Although they do not prove that living tubercle bacilli are present, the evidence is in favor of such a hypothesis. On the contrary, their absence does not prove the absence of bacilli. Certainly this is true for the younger ages, and the gradual disappearance of these giant cells suggests healing of the infection. Although many resemble the foreign body variety, most of them are typical tubercle giant cells. If the presence of living tubercle bacilli in tubercles is indicated by the presence of these giant cells alone, most tubercles contain living bacilli for four or five years, many for eight or ten years and a few for thirteen years.

While this discussion has been confined to average-sized healing tubercles, problems of greater importance are encountered in the slowly progressive lesions. The changes here may be several. Important among these is the slowly overflowing tubercle. Here the encapsulation is slower than the growth of the bacilli, and a progressive lesion develops. Bacilli enter the finer bronchioles and spread to adjacent lobules or into larger bronchi and involve other regions, producing infiltrates similar to the coarse and fine dissemination observed by Loeschcke (*Beitr. z. Klin. d. Tuberk.* **68**:251, 1928). This happens in primary infections of young adults in which the capsules develop more slowly than in children. L. Du Nouy (Biological Time, New York, The Macmillan Company, 1937) has noted that growth of body cells is retarded with increasing age. Another significant change is the focal softening of the capsule, perhaps due to the action of bacilli or to a local hypersensitiveness. This ends as a breach in the wall, with a spread of the bacilli into the surrounding tissues, or as an actual rupture into a bronchus. Rarely a blood vessel may be involved, with wide dissemination of the infection. This may happen in the local lesion or in the secondary lesions of the lymph nodes. The local lesion may surround a bronchus and rupture into the bronchus at the site of entry. This usually leaves a small excavation.

As a result of these destructive changes and the survival of the tubercle bacilli, 74.6 per cent of young patients in this series with accurate histories of gross contact had an insidious endogenous spread of the bacilli, culminating in a clinical episode on the average ten years after the initial infection and death after another three and a half years.

DISCUSSION

I. DAVIDSOHN: Is there a difference in the structure of these tubercles in the white and Negro races at corresponding periods of evolution?

H. G. WELLS: How do you determine the age of development of the tubercles?

S. ROSENTHAL: I am interested to know how you determine that pulmonary tuberculosis arises from a healed primary focus.

F. D. GUNN: What bearing has an acute infection, such as bronchitis, on the initiation of active pulmonary tuberculosis?

H. C. SWEANY: There are distinct differences between the evolution of tuberculosis in the white and that in the Negro race. This is especially true with the Negro recently introduced from the South. Those who have lived in Chicago for some time react more like members of the white race. In every one of these selected 100 cases there is a clearcut history of contact with an actively tuberculous patient. Many criteria were used in evaluating the age of a tubercle. In some forms of pulmonary tuberculosis only the principal ways of spread can be determined; in others, a very definite way. Many tubercles remained healed or will heal unless some other infection or a constitutional disturbance, such as pregnancy, occurs. These accidental conditions have an important bearing.

H. G. WELLS: Esmond R. Long at the Henry Phipps Institute of the University of Pennsylvania has compared the evolution of tuberculosis in the white and Negro races. In the aboriginal Negro tuberculosis develops as in a guinea pig. Jamaica Negroes who have lived in the North since the sixteenth century react like the white race. When pulmonary tuberculosis develops in the Negro, the number of tubercle bacilli expectorated daily exceeds greatly that in the case of Caucasians.

A STATISTICAL EVALUATION OF ENVIRONMENTAL CHANGE IN THE ONSET OF SCARLET FEVER. W. F. PETERSEN and ALVIN MAYNE.

The records of the Department of Health of Chicago on scarlet fever for the years 1934 and 1935 were examined, and the date of the onset of the rash in each case was tabulated. This date could be definitely determined in approximately 90 per cent of the cases. Quite apart from the seasonal trends, the graphs revealed definite periodic accentuation. Such predominance when referred to in the literature of epidemiology is usually accepted as due to chance.

The material was studied statistically with reference to daily barometric pressure, temperature and humidity, and it was found that a definite association exists, with the precipitation of more cases following an increase in barometric pressure. In this analysis the twenty-four lag revealed the highest correlations.

DISCUSSION

I. DAVIDSOHN: In connection with all of these conditions the epidemic factor may be important. Would this influence be shown in the comparisons? The erythrogenic factor has been selected in plotting these statistics. Would the same influencing factors be demonstrated by a study with the Dick test?

W. F. PETERSEN: J. S. Howe has found the same factors influencing other skin tests. The epidemic factor has not been investigated. Streptococci are present in the throat during the period of incubation, and when the opportunity for penetration of tissue arises the symptoms begin.

BACILLEMIA IN EXPERIMENTAL TUBERCULOSIS: A PRELIMINARY REPORT. JOHN S. HOWE.

Experimental tuberculosis was produced in dogs by injecting intravenously large doses of virulent human tubercle bacilli, suspended in kaolin, mineral oil and saline solution. This produced lesions limited largely to the lungs and tending to heal or to progress slowly. Tuberculous abscesses were produced in dogs by injecting similarly suspended tubercle bacilli into the thoracic wall. These lesions tended to discharge for a time and then heal.

In all, 10 dogs were given intravenous injections and 3 dogs subcutaneous injections in the wall of the chest with doses of tubercle bacilli ranging from 3 to 20 mg. The femoral artery of each dog was punctured daily, with sterile precautions, and from 3 to 5 cc. of arterial blood was withdrawn and injected directly into a guinea pig, either intraperitoneally or subcutaneously. In one series the inoculation of the guinea pig was controlled by culture of a part of the blood sample on Löwenstein's medium. All the guinea pigs were tested with tuberculin before inoculation with the blood and at intervals afterward up to three months, when all were killed and examined. The presence of tuberculosis was established on the basis of the characteristic gross and microscopic lesions, supported by a positive tuberculin test and the results of a microscopic examination of preparations stained for tubercle bacilli.

In the course of daily observations over periods ranging from two to three months, 8 of the 10 dogs given intravenous injections showed bacillemia in at least one blood sample. Two of these dogs died with progressive pulmonary tuberculosis and had frequent periods of marked bacillemia. The other 6 dogs showed a tendency toward healing of their tuberculous lesions with sporadic periods of bacillemia. The 3 dogs with abscesses of the wall of the chest showed a tendency toward healing of their lesions, with sporadic periods of bacillemia in 2 of the dogs.

These periods of bacillemia show some tendency to coincide in time in animals observed over the same period and in some instances correspond in time to clinical episodes in patients with tuberculosis under observation at the same time. A projection of these periods of bacillemia on a meteorograph for the period of observation shows a rather definite tendency for bacillemia to occur with severe meterologic disturbances, particularly with polar infalls characterized by rapidly rising barometric pressure and falling temperature.

Further work is in progress in an attempt to determine more definitely the factors operating to produce or prevent bacillemia in experimental and in clinical tuberculosis.

DISCUSSION

F. D. GUNN: Are the episodes of bacillemia due to a drop in temperature?

S. ROSENTHAL: Bacillemia has been observed in guinea pigs before the tuberculin reaction appears but not after.

J. S. HOWE: The bacillemia does not seem to be a direct effect of change in temperature. I have not studied particularly the relation of bacillemia to the tuberculin reaction but have noted bacillemia in the presence of the tuberculin reaction.

Book Reviews

Phenomenon of Local Tissue Reactivity and Its Immunological, Pathological and Clinical Significance. By Gregory Shwartzman, M.D., Bacteriologist, the Mount Sinai Hospital, New York. Foreword by Jules Bordet, M.D., Paris. Pp. 461, with 67 illustrations and 1 color plate. Price, $7.50. New York: Paul B. Hoeber, Inc., 1937.

This book is the outcome of an experiment which took place in September 1927. Shwartzman injected 0.25 cc. of a filtrate of a culture of Bacillus typhosus into the skin of the abdomen of a rabbit. At the site of the injection the skin showed no reaction whatsoever or only a very slight redness. However, when twenty-four hours later the same filtrate was injected intravenously, there developed on the site of the first injection, in about four hours, a severe hemorrhagic lesion. This record looks like that of a rather simple experiment, but the results of that experiment were significant and their influence far reaching. Bordet expresses it well in his introduction: "The discovery of the phenomenon was totally unexpected, it must be acknowledged, for if there is any field which has been minutely investigated from every point of view and conscientiously searched it is that of the reactions of the organism to bacterial products. One could not have suspected that in this field secrets still remained unraveled and surprises were in store for us.

"It may seem strange that the phenomenon to which the name of Shwartzman remains attached was not discovered earlier, since denoting itself by accidents, hemorrhagic in nature, it gives rise to striking and especially conspicuous manifestations, and since the conditions necessary for its reproduction are in all probability frequently encountered experimentally and in the course of spontaneous infections."

The book is a summary of the work on the phenomenon of local tissue reactivity, better known as the Shwartzman phenomenon. Shwartzman defines the phenomenon as being "contingent upon the elicitation of a certain state of reactivity by means of the bacterial active principles described. This state represents a modified response to the injurious effect of toxic principles in the blood stream and apparently constitutes a hitherto unknown mechanism of production of severe injury in the animal cell."

The monograph analyzes the contributions not only of the original discoverer of the phenomenon and of his associates but also of all the writers on the subject up to the beginning of 1936. It also includes many unpublished observations by Shwartzman.

The book is divided into thirteen chapters. The introductory chapter deals with general technical considerations. The second chapter lists the species of bacteria and a metazoon, Ascaris lumbricoides, that were shown to be able to produce the phenomenon. The influence of various physical and chemical factors on the active principles is discussed in the third chapter. The following chapter reviews the accumulated data which established beyond doubt the antigenic nature of the skin preparatory and reactive factors. These factors can be neutralized specifically and according to the law of "multiple proportions"; they possess "strain" and "variant" specificity.

The discussion of immunity to the phenomenon in the fifth chapter includes observations on the refractoriness of about 20 per cent of rabbits and on the production of specific and nonspecific artificial immunity. The behavior of other animals (guinea pigs, goats, horses, mice and rats) and the conditions under which passive immunity against the phenomenon can be produced are described. In the sixth chapter Shwartzman marshals convincing observations to prove that inflammation plays no role in the phenomenon. The production of the characteristic

hemorrhagic lesion in tissues and organs other than the skin, various modifications of the procedure and the use of bacteria instead of filtrates as the preparatory factors are the subject of chapter 7.

The next chapter is an account of the dramatic results following injection of the preparatory factors into tumors of guinea pigs, mice and rats.

That the significance of the Shwartzman phenomenon extends beyond the realm of bacterial filtrates is evidenced from data presented in the ninth chapter. Mixtures of certain animal and bacterial proteins with homologous antiserums may act as reacting factors in rabbits prepared with intradermal injections of bacterial active principles. The action may be due to a toxic quality liberated through the interaction between the antigen and the antibody. A few other substances capable of producing the reaction are listed. The tenth and eleventh chapters synthesize some of the fundamental features of the work on the phenomenon: The resemblance of the active principles to true exotoxins and the differences from the endotoxins are brought out convincingly. It is emphasized that all findings point against any relationship with the Arthus phenomenon. The immunologic, pathologic and clinical significance of the phenomenon is presented in the twelfth chapter, and its application to treatment of certain human conditions is dealt with in the last chapter.

The bibliography is listed on fifteen pages. The indexes of authors and subjects conclude the volume. The illustrations and print are excellent.

The style is pleasing; the presentation of difficult and intricate subjects is lucid.

This monograph is not only a source book of facts, but, what is more important, a source book of stimulation and inspiration. Those who want suggestions and ideas will find them. It is a door to new and as yet not fully explored regions. The immunologist, the bacteriologist, the pathologist and the scientifically thinking physician can hardly afford not to read this book.

Let Jules Bordet conclude this review with the same fitting words with which he finished the preface: "A debt of gratitude is due to Dr. Shwartzman for having discovered the phenomenon described in this book; a debt of gratitude is also due him for having proceeded with his researches on this important problem with the great precision which he alone could achieve."

Legal Medicine and Toxicology. Thomas A. Gonzales, M.D., Acting Chief Medical Examiner of the City of New York; Associate Professor of Forensic Medicine, New York University College of Medicine; Lecturer on Criminological Medicine, New York Police Academy. Morgan Vance, M.D., Assistant Medical Examiner of the City of New York; Associate Professor of Forensic Medicine, New York University College of Medicine; Lecturer in Forensic Medicine, College of Physicians and Surgeons, Columbia University; Lecturer on Criminological Medicine, New York Police Academy. Milton Helpern, M.D., Assistant Medical Examiner of the City of New York; Assistant Professor of Forensic Medicine, New York University College of Medicine; Lecturer in Legal Medicine, Cornell University Medical College; Lecturer on Criminological Medicine, New York Police Academy. With a foreword by Harrison S. Martland, M.D., Chief Medical Examiner, Essex County (Newark), N. J.; Professor of Forensic Medicine, New York University College of Medicine. Pp. xxxiii and 754, with 244 illustrations. Price, $10. New York: D. Appleton-Century Company, Inc., 1937.

The subject matter of the broad field of forensic medicine, which means literally the medicine of the forum, falls rather naturally into two main subdivisions: (1) the law as it relates to the physician, his qualifications and right to practice medicine, his duties and obligations to the public and his relations to fellow members of the medical profession; (2) medicine as applied to law and legal procedures. The first, known as medical jurisprudence, is the law of medicine; the second, to which the term "legal medicine" in the strict sense might well be limited, is the medicine of the law.

To cover both aspects of forensic medicine would require a combination of a medical and a legal library of many imposing tomes. In the more restricted field of legal medicine a complete presentation of the relations of the fundamental medical sciences and of pertinent nonmedical sciences would require an encyclopediac system. Fortunately, the technical procedures of the auxilliary sciences that come into use in medicolegal investigations can be left to books dealing specifically with such procedures, of which there are many in each discipline, and their interpretation. The chief problem, then, in the preparation of a one volume book on legal medicine is one of selecting what to use and what to omit.

In "Legal Medicine and Toxicology" by Gonzales, Vance and Helpern this selection has been well done. The first sixty-five pages are divided into five brief chapters that contrast the coroner and medical examiner systems and discuss in turn: the relations of the medical examiner to other governmental agencies, such as the health department, the prosecutor and the courts; the identification of the living and of the dead body, with a listing of the times of fusion of the various centers of ossification; the technic of the medicolegal autopsy, and the signs of death. Then follows a chapter of twenty-six pages devoted to sudden death due to natural causes; this contains a three page classification of the causes of unexpected death.

Ten chapters are devoted to a discussion of death due to trauma, under the headings of blunt force, stab and incision wounds, bullet wounds, asphyxia and deaths due to the physical agencies of heat, cold, electricity and radiation. Three chapters are devoted to pregnancy, abortion and infanticide. Impotence, rape and related sexual topics comprise two brief chapters. Microscopic and serologic examinations of medicolegal import are given three chapters. Sketchy discussions of insanity, of the rights of physicians and of problems relating to insurance seem to belong in the field of medical jurisprudence, where they could be more fully discussed. What might at first glance appear to be a disproportionate share of the book is given to toxicology, but the greater part deals with the anatomic effects of poisons, the aspect of toxicology that most concerns the medicolegal pathologist.

A sighificant feature of this volume is that it is based on the experience of the former deputy medical examiner, who is now chief medical examiner, of New York city, and of two colleagues who were associated with him under the former and first chief medical examiner. The treatise is evidence of the character of work that may be expected of a well organized medical examiner system. The book is profusely illustrated with photographs from the collection of the New York medical examiner's office. These photographs have been well reproduced and show what they are supposed to show. They are not "pretty," but violent death is a matter of stern reality, not esthetics. Those familiar with the work of Charles Norris in the organization and direction of the office of chief medical examiner of New York city from the establishment of the office in 1918 to his death in 1935 are pleased that his three former pupils and associates in that office have dedicated their book to his memory.

Recent Advances in Pathology. Geoffrey Hadfield, M.D., F.R.C.P. (London), Professor of Pathology, University of London, and Pathologist to St. Bartholomew's Hospital, London. Lawrence P. Garrod, M.A., M.D., B.Ch. (Cambridge), F.R.C.P. (London), Professor of Bacteriology, University of London; Bacteriologist to St. Bartholomew's Hospital, and Examiner in Pathology, University of Cambridge. Third edition. Cloth. Pp. 420, with 65 illustrations. Price, $5. Philadelphia: P. Blakiston's Son & Co., Inc., 1938.

This book, entitled "Recent Advances in Pathology," could, without much exaggeration, be called a text of pathology covering certain specified subjects. Since the authors did not choose to cover the whole field of pathology, they exercised choice of subjects within a number of fields, and their choice may at times seem arbitrary, but that cannot be avoided in a book of this compass. They presuppose a working acquaintance with pathology, but nevertheless they lead up

to the "advances" which they discuss from older knowledge and views, so that the book becomes valuable not only to the professional pathologist but to any intelligent clinician who refuses, as every clinician should do, to remain "dated" in his knowledge of pathology. To the professional pathologist whose own work has led him to specialize heavily in any field, the book affords competent guidance to a renewal of acquaintance with other fields.

It is written in narrative style, which makes for easy reading. Little detailed pathologic anatomy is given except in a few instances in which new and definite facts have been added to the old. There is a heavy accent on pathologic physiology, on symptomatology and on the course and progress of disease, which is to be highly commended as a proper method of presentation of advanced pathology.

Beginning with several general discussions of resistance to infection and of experimental research in cancer, the authors take up the various organic systems systematically. Thus the heart and arteries, the respiratory system, the digestive system, the central nervous system and the ductless glands are treated. As the contribution to the pathology of the kidneys, Bright's disease and nephrosis are well discussed. There is a chapter on deficiency diseases; also one on the reticulo-endothelial system and reticuloses.

To mention a few details, the reviewer, among other things, likes the way in which the phrase "differentiates into" is used in discussion of cell potency. When mesenchymal cells are mentioned, stress is laid on the relationship of the differently appearing cells, and various names are rehearsed but so given as to make it appear as though they did not designate distinct entities but developmental phases of similar cells. Sympathy is expressed with the attempts made to classify reticuloses. The chapter on nephrosis and edema is impressive.

It is good to see that at least inklings of the variegated significance of the word "growth" are given when it is used. There are so many meanings for this word that much confusion could be avoided if proper limitations were used, for there is growth in weight, in size, in number, in complexity and so on. American authors in particular are great offenders in this important regard.

Not the least interesting part of the method of handling the material is that many questions are asked and many answers left open but expressed in such a way that they stimulate the desire to investigate, which the reviewer cannot help but feel is a superior method of presentation.

Naturally, there is disagreement of details, but progress is helped that way and no specific criticism can be given of it.

The references are sufficient and are placed at the end of the treatment of a subject or of the chapter. There are not too many in the text, and thus the continuity of reading is not too much interrupted.

It is a pleasure to recommend the book to both pathologists and clinicians.

The Treatment of Laboratory and Clinical Data: An Introduction to Statistical Ideas and Methods for Medical and Dental Workers. Donald Mainland, M.B., Ch.B., D.Sc. (Edinburgh), Professor of Anatomy, Dalhousie University, Halifax, Nova Scotia, Canada. Pp. 340, with 23 text figures. Cloth. Price, $3.60. Edinburgh and London: Oliver & Boyd, 1938.

As indicated in the title, the main object of this book is to present ideas and some methods to assist the medical and dental clinician in evaluating the results of his own observations and to help him in the critical reading of the statements of other observers. The book also aims to serve as an elementary introduction to this subject for laboratory workers in the fields of medical and dental anatomy, pathology and physiology. The expressed purposes appear to be well served by this book, which is recommended to the increasing number of medical men who desire to know to what extent the application of statistical ideas may be helpful to them in their work.

The book does not attempt to be exhaustive nor to go further into the development of formulas than is necessary to show their reasonableness. The method of exposition is to work from examples to general principles and technic. The

examples used are largely such as are commonly met with in the clinic and laboratory, and the methods emphasized are those applicable to the handling of clinical data when only a limited number of observations may be available. The author appears to have succeeded in anticipating most of the questions likely to arise in the mind of the reader and in making clear that any analysis of data must be secondary to proper planning of experiments or critical selection of material.

It seems unfortunate that it should be necessary to ask the reader to consult another book for reference tables which, if included, would have added but little to the size of the present work.

Practical Bacteriology, Haematology and Animal Parasitology. By E. R. Stitt, M.D., Sc.D., L.L.D., Rear Admiral, Medical Corps, and Surgeon General, U. S. N. (Rtd.); Paul W. Clough, M.D., Chief of Diagnostic Clinic, Johns Hopkins Hospital, and Associate in Medicine, Johns Hopkins University, and Mildred C. Clough, M.D., Formerly Fellow in Bacteriology and Instructor in Medicine, Johns Hopkins University. Ninth edition. Cloth. Price, $7. Pp. 961, with 208 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1938.

Stitt's "Practical Bacteriology, Blood Work and Animal Parasitology" appeared in eight editions. This long life proved its use and value. It has now been entirely rewritten and reset to make a work of 961 pages under the title "Practical Bacteriology, Haematology and Animal Parasitology." The work has been an exceedingly usable one and at the same time has been almost an encyclopedia of clinical pathology. Every subject is thoroughly discussed from both the technical and the clinical aspect, as should be done in a textbook of clinical laboratory medicine.

In this edition, Dr. Stitt has had the collaboration of two excellent clinicians, Dr. Paul Clough and Dr. Mildred Clough, who also are thoroughly versed in all phases of clinical and laboratory work.

The illustrations are excellent. The composite color plate of blood cells taken from Clough's "Diseases of the Blood" is the best single plate the reviewer has seen in any book on hematology. The utilization of even the inside covers for information of practical value is to be commended. This book cannot be recommended too highly to both the clinician and the laboratory worker.

A Textbook of Hematology. By William Magner, M.D., D.P.H., Pathologist, St. Michael's Hospital, Toronto, and Lecturer in Pathology, University of Toronto. Cloth. Price, $4.50. Pp. 395, with 26 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1938.

With the recent greatly increased interest in hematology, a number of new books on blood diseases have appeared. For the most part these have done little to clarify the disorders of the blood for the average student and practitioner. All the common abnormalities of the blood depend on relatively few simple principles. This book is one of the first to attempt "to present the subject of hematology in a manner acceptable to practicing physicians as well as those primarily interested in the study of disease by laboratory methods." The arrangement of the subject matter follows a logical sequence, beginning with a discussion of hemopoiesis and the different types of cells and hemoglobin. The discussion of laboratory methods is good. The anemias are divided into the dyshemopoietic, the posthemorrhagic and the hemolytic.

This book is a creditable attempt to simplify the exposition of hematology. There are few illustrations. Both the colored plates and the photomicrographs are poor.

Books Received

THE FIFTY-THIRD ANNUAL MEDICAL REPORT OF THE TRUDEAU SANATORIUM AND THE THIRTY-THIRD MEDICAL SUPPLEMENT FOR THE YEAR ENDING SEPTEMBER 30, 1937, TOGETHER WITH THE TWENTY-FIRST COLLECTION OF THE STUDIES OF THE EDWARD L. TRUDEAU FOUNDATION FOR RESEARCH AND TEACHING IN TUBERCULOSIS, 1937.

THE SARANAC LABORATORY FOR THE STUDY OF TUBERCULOSIS OF THE EDWARD L. TRUDEAU FOUNDATION: REPORT OF THE DIRECTOR AND FINANCIAL REPORT FOR THE YEAR ENDING SEPTEMBER 30, 1937. REPRINTS OF SCIENTIFIC PAPERS. Saranac Lake, N. Y.: The Saranac Lake Academy of Medicine, 1937.

THE BIOLOGY OF ARTERIOSCLEROSIS. M. C. Winternitz, M.D., R. M. Thomas, M.D., and P. M. LeCompte, M.D. Cloth. Pp. 144, with 116 illustrations. Price $4. Springfield, Ill.: Charles C. Thomas, Publisher, 1938.

LA TUBERCULOSE PULMONAIRE CHEZ LES SUJETS APPAREMMENT SAINS ET LA VACCINATION ANTI-TUBERCULEUSE. L. Saye. Monographies de l'Institut Pasteur. Paper. Pp. 254, with 88 figures. Price 60 francs. Paris: Masson & Cie, 1938.

LES MENINGO-NEUROBRUCELLOSES. Henri Roger and Yves Poursines. Paper. Pp. 248. Price 45 francs. Paris: Masson & Cie, 1938.

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